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2.	Patent application number *(The Patent Office will fill in this part)*	0400720.9 — 14 JAN 2004
3.	Full name, address and postcode of the or of each applicant (*underline all surnames*)	**STYLACATS LTD.** Cheshire Manufacturing Park, Oil Sites Road, Ellesmere Port, Cheshire, CH65 4HF.
	Patents ADP number (*if you know it*)	7910 227002
	If the applicant is a corporate body, give the country/state of its incorporation	ENGLAND
4.	Title of the invention	NOVEL FERROCENE-BASED PHOSPHORUS CHIRAL PHOSPHINES.
5.	Name of your agent (*if you have one*)	**W. P. THOMPSON & CO.**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Coopers Building, Church Street, Liverpool, L1 3AB
	Patents ADP number *(if you know it)*	0000158001

		Country *(if you know it)*	Priority application number *(if you know it)*	Date of filing *(Day/month/year)*
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

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8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'yes' if:* *a) any applicant named in part 3is not an inventor, or* *b) there is an inventor who is not named as an applicant, or) any named applicant is a corporate body.* *See note (d)*	YES

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Continuation sheets of this form	
Description	58
Claims(s)	10
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
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Request for substantive examination *Patents Form 10/77*)	
Any other documents *(Please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature W.P. Thompson & Co. Date 13/01/2004

12. Name and daytime telephone number of person to contact in the United Kingdom: T.L. BRAND. 0151-709-3961

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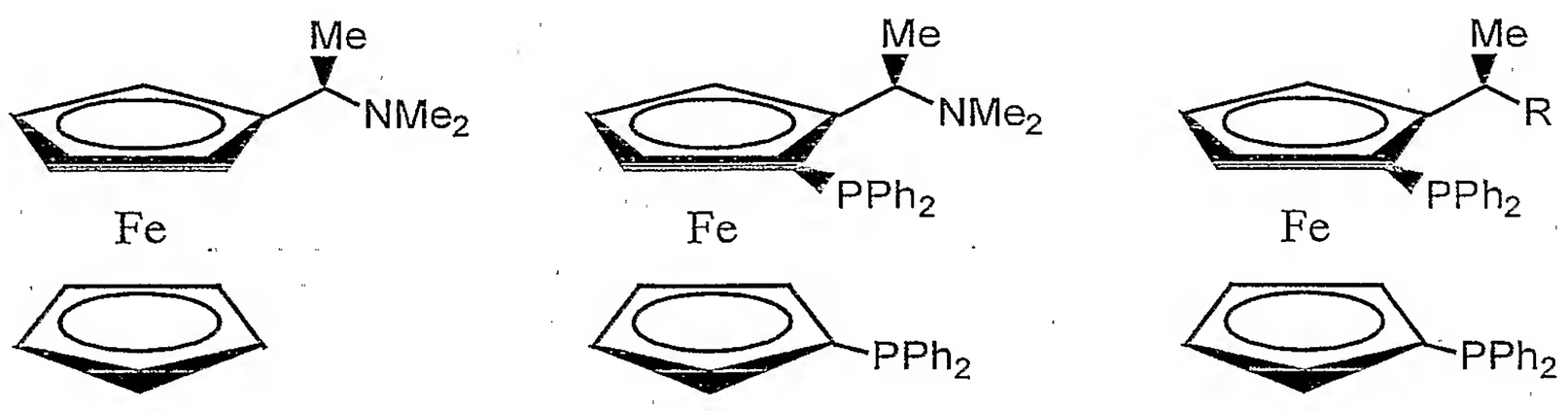
P4082646

DUPLICATE

NOVEL FERROCENE-BASED PHOSPHORUS CHIRAL PHOSPHINES

This invention relates to novel ferrocene-based phosphine ligands incorporating up to three elements of chirality, planar chirality, chirality at phosphorus, and optionally chirality at carbon, and methods for their preparation. In addition, this invention relates to the metal-ligand complexes that can be used as catalysts or precatalysts for asymmetric transformation reactions to generate products of high enantiomeric excess.

Ferrocene as a backbone for diphosphine ligands was introduced by Kumada and Hayashi based on the pioneering work of Ugi related to the synthesis of enantiopure substituted ferrocenes[1]. A number of these ligands are shown below:

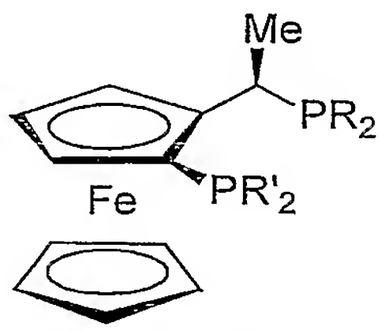


Ugi's Amine PPFA R = Me_2N, BPPFA
R = OH, BPPFOH

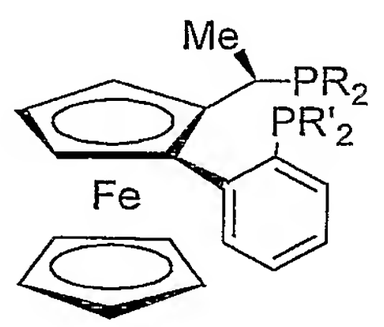
Ppfa as well as bppfa and bppfoh proved to be effective ligands for the catalysis of a variety of asymmetric transformations. From this starting point, many chiral

ferrocene-based bisphosphine ligands with a range of structural variation have been developed in the last few years.

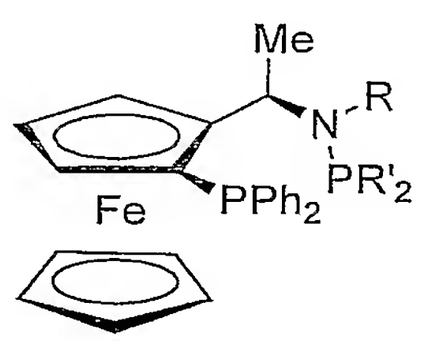
Certain types of known ligands exhibit both planar and carbon chirality:



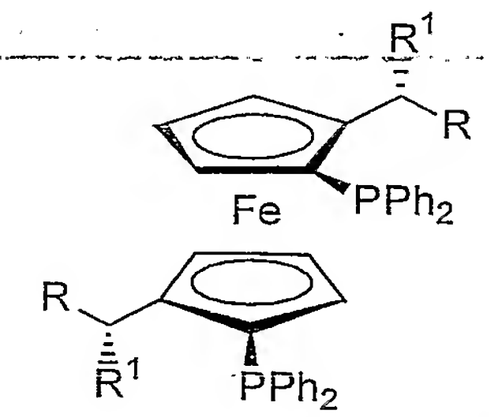
Josiphos: R = Cy, R' = Ph
PPF-tBu$_2$: R = t-Bu, R' = Ph
Xyliphos: R = 3,5-Me$_2$Ph, R' = Ph
cy$_2$PF-Pcy$_2$: R = R' = Cy



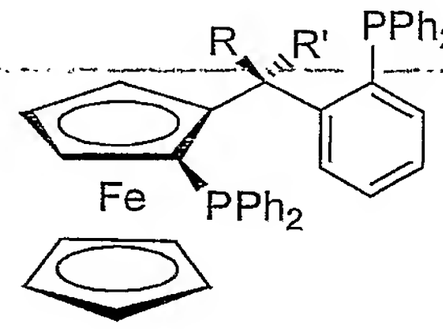
Walphos



BoPhoz

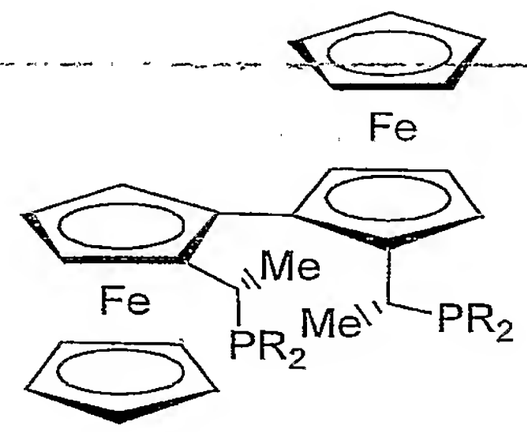


Mandyphos (FERRIPHOS)



Taniaphos

1a: R = H, R' = NMe$_2$
1b: R = OMe, R' = H



TRAP

Togni and Spindler have reported a class of non-C_2-symmetrical ferrocene-based bisphosphines: the Josiphos-type ligands.[2] Josiphos ligands are in widespread commercial use, having been found effective for Rh-catalyzed hydrogenation of α-acetamidocinnamate, dimethyl itaconate, and β-ketoesters. Because the two phosphine groups are introduced into the ligand in consecutive steps with high yields, a variety of ligands are available with widely differing steric and electronic properties. The ligands have already been applied in three production processes, [3] several pilot processes and many other syntheses. For

example, PPF-tBu2, a Josiphos type ligand with a di-(tert-butyl)phosphino group, has been applied as the ligand in asymmetric hydrogenation for commercial synthesis of (+)-biotin.[4] Another notable example is the application of XyliPhos in Ir-catalyzed hydrogenation of imine for the synthesis of the herbicide (S)-metolachlor. [5]

Bophoz is a combination of a phosphine and an aminophosphine and is prepared in 3 steps from ppfa with high overall yields. [6] The ligand is air stable and effective for the hydrogenation of enamides, itaconates and α-keto acid derivatives. As observed for several ligands forming seven-membered chelates, high activities can be reached and TONs up to 10,000 have been claimed. The full scope of this modular ligand class has not yet been explored.

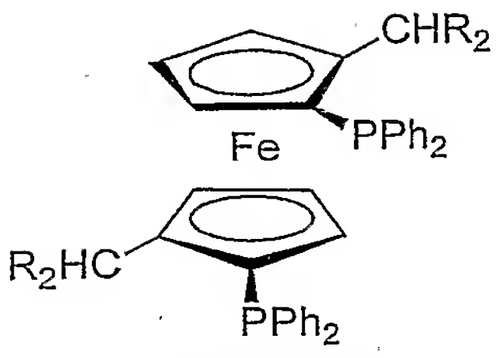
A class of non-C_2-symmetrical, ferrocene-based 1,5-diphosphine ligands, Taniaphos, has been developed by Knochel. [7,8] Compared to the Josiphos ligands, Taniaphos has an additional phenyl ring inserted at the side chain of the Ugi amine. Taniaphos gave excellent results in Rh- and Ru-catalyzed asymmetric hydrogenation. The configuration of α-position of Taniaphos plays an important role in the enantioselectivities and activities. The Taniaphos 1b with αS configuration leads to higher enantioselectivities and activities than 1a with αR configuration in a wide range of asymmetric transformations. [8]

Weissensteiner and Spindler have reported a series of structurally different ferrocene-based 1,5-diphosphine ligands, Walphos. [9] Like Josiphos, Walphos is modular and is also made from the Ugi amine. It shows promise for the enantioselective hydrogenation of olefins and ketones.

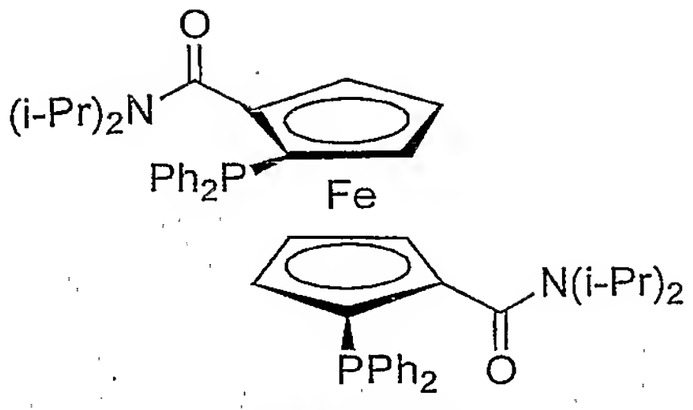
Mandyphos is a bidentate version of ppfa with C_2 symmetry, where in addition to the PPh_2 moieties, R and R' can be used for fine tuning the functionality of the ligand. [10] The scope of this ligand family has not yet been fully explored, but preliminary results indicate high enantioselectivities for the Rh-catalyzed hydrogenation of enamides, itaconates and enol acetates.

The TRAP ligands developed by Ito[11] form 9-membered metallocycles. However, it is not clear whether the cis-isomer, present in small amounts, or the major trans-isomer is responsible for the catalytic activity. Up to now only a few different PR2 fragments have been tested, but it is clear that the choice of R strongly affects the catalytic performance. The Rh complexes work best at very low pressures of 0.5 ± 1 bar and effectively reduces indole-derivatives, enamides and itaconic acid derivatives.

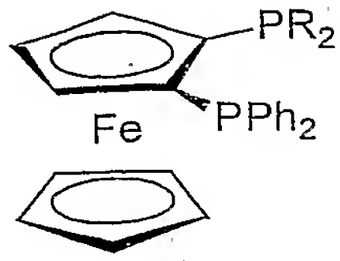
Another class of known ligands exhibit only planar chirality:



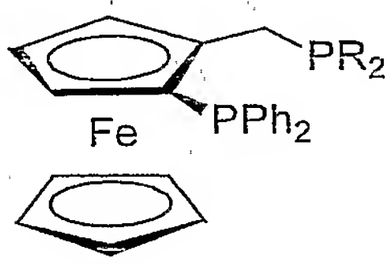
ferroPHOS



JAFAPhos



2



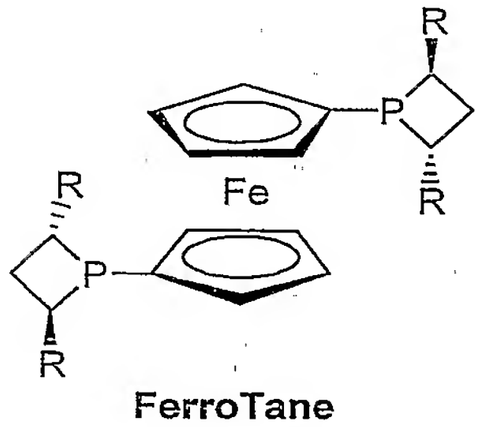
3

Kang reported the C_2-symmetry FerroPHOS with only planar chirality. [12] FerroPHOS ligands are air-stable and are very efficient for the asymmetric hydrogenation of various dehydroamino acid derivitives (up to 99% ee).

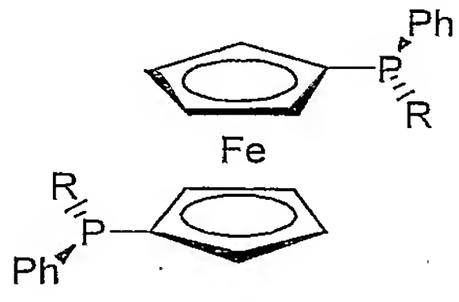
Another C_2-symmetry planar chiral diphosphine, JAFAPhos, has been developed by Jendralla. [13] JAFAPhos gave excellent results in asymmetric hydrogenation, allylic alkylation, Grignard cross coupling and aldol reactions.

Kagan reported plane chiral ferrocene-based bisphosphorus ligands 2 and 3, [14] and up to 95% ee's have been obtained in asymmetric hydrogenation of dimethyl itaconate using these ligands as catalyst.

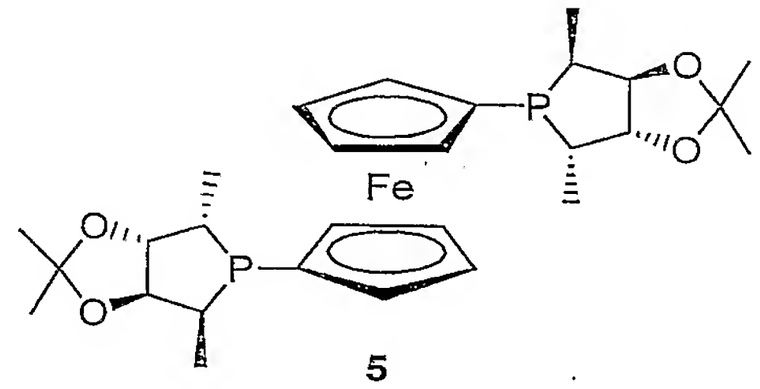
Another class of known diphosphine ligands exhibit chirality only at the phosphorus atoms:



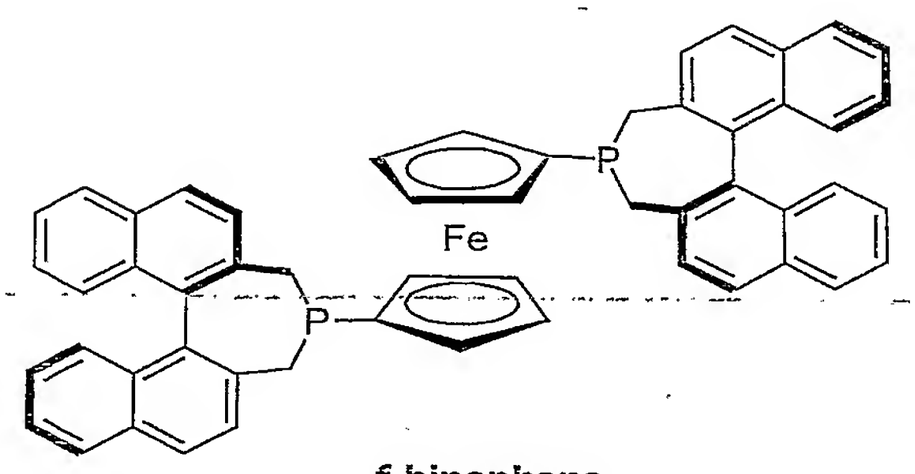
FerroTane



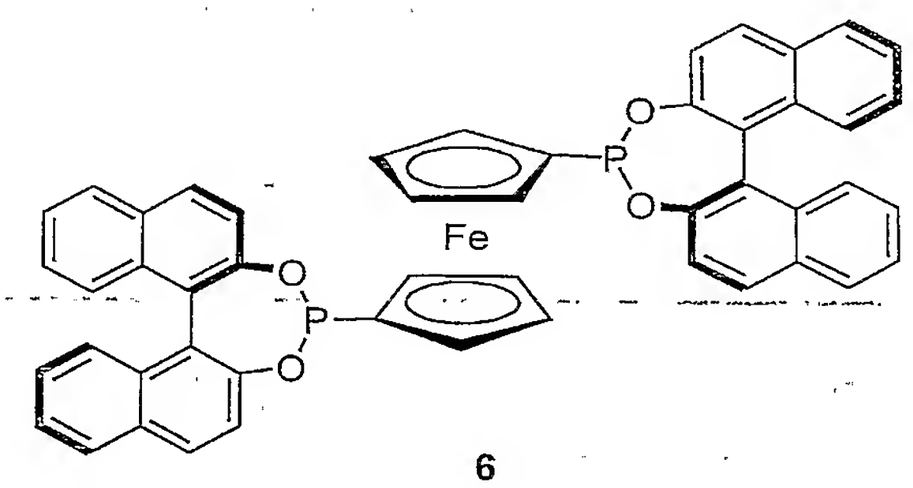
4a: R = o-anisyl
4b: R = 1-naphthyl



5



f-binaphane



6

5

The synthesis of chiral 1,1'-bis(phosphetano) ferrocenes (FerroTANE) has been independently reported by Marinetti [15] and Burk. [16] FerroTANE has been successfully applied in Rh-catalyzed hydrogenation of itaconates and (E)-β-(acylamino) acrylates. [17]

10

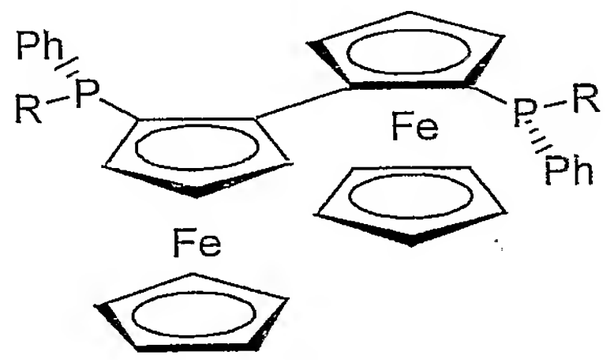
Mezzetti [18] and van Leeuwen [19] have independently reported P-chiral ferrocenyl bisphosphines 4a and 4b. These two ligands have shown excellent enantioselectivities (up to 99% ee) for asymmetric hydrogenation of α-dehydroamino acid derivatives.

15

Zhang has reported a 1,1'-bis(Phospholanyl) ferrocene ligand 5 with ketal substitutes at the 3 and 4 positions. [20] The ligand has shown excellent enantioselectivities in hydrogenation of β-dehydroamino acid derivatives. The ketal groups of the ligand are important for achieving the high enantioselectivity, since the corresponding ligand without ketal groups only provides moderate ee's. Zhang has also developed a 1,1'-bis(dinaphthophosphepinyl) ferrocene ligand, f-binaphane, which has been successfully applied in Ir-catalyzed hydrogenation of acyclic arylimines. [21]

Reetz has developed a binaphthol-derived ferrocene-based bisphosphonite ligand 6, [22] which has shown excellent reactivities and enantioselectivities in Rh-catalyzed hydrogenation of itaconates and α-dehydroamino acid derivatives.

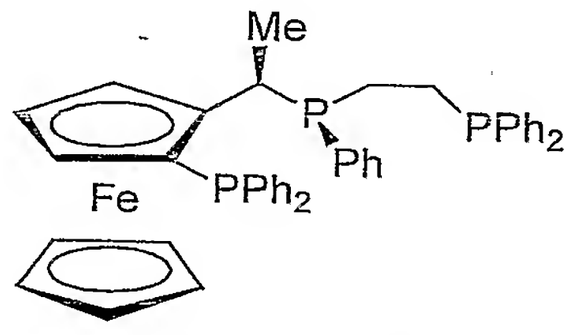
Another class of known ligands exhibits both planar and phosphorus chirality:



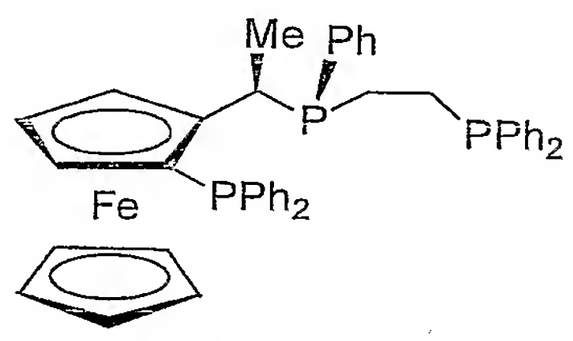
7a: R = 1-naphthyl
7b: R = 2-biphenylyl

Van Leeuwen has reported ferrocene-based bisphosphines combining planar and phosphorus chirality 4a and 4b. [23] These two ligands have shown excellent enantioselectivities (up to 99% ee) for asymmetric allylic alkylations.

Thus, most of the known ferrocene-based diphosphines contain planar and carbon chirality, only planar chirality or only phosphorus chirality. More recently, Togni reported the first tridentate ferrocene-based phosphine ligand 12 combining planar, phosphorus and carbon chirality. [24]



$(R)_C$-$(S)_{Fe}$-$(S)_P$-12



$(R)_C$-$(S)_{Fe}$-$(R)_P$-12

It would be advantageous to design bisphosphine ligands incorporating up to three elements of chirality, planar chirality, chirality at phosphorus, and chirality at carbon for use in enantioselective catalysis. It would also be advantageous to design ligands that exhibit three different types of chirality; carbon, planar and phosphorus.

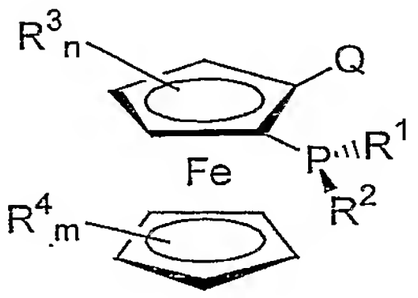
According to the present invention there is provided a ferrocene-based phosphine having up to three elements of chirality, planar chirality, chirality at phosphorus, and optionally chirality at carbon.

The invention further provides a ferrocene-based diphosphine having planar, phosphorus and carbon chirality.

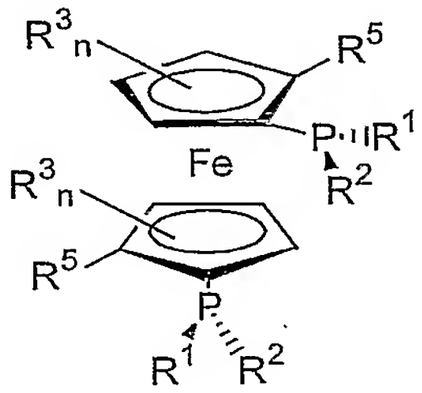
Ligands according to the invention have particular advantages over prior art ligands because the provision of three chiralities allows the designer of a ligand greater scope than has hitherto been the case to design ligands for a particular purpose.

Examples 30 to 34 below demonstrate matching and mismatching of catalyst and substrate.

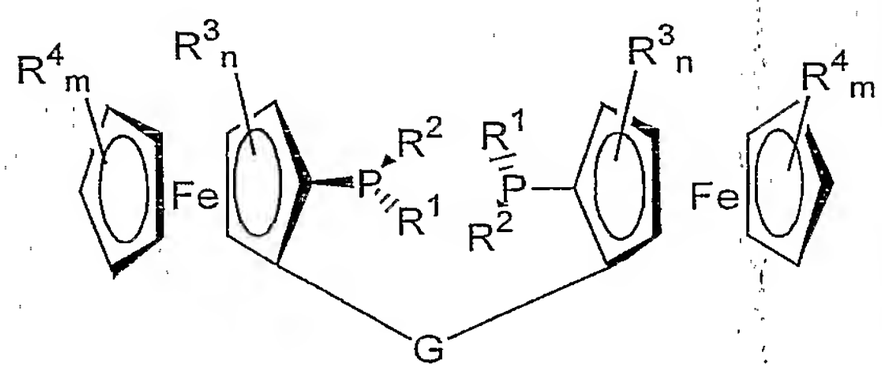
Preferred ligands in accordance with the invention are selected from ligands having Formula (I), (II) or (III):



(I)



(II)



(III)

wherein

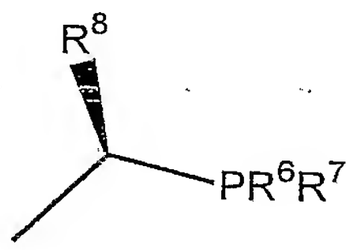
R^1 and R^2 are different from each other, and are independently selected from substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

R^3 and R^4 are the same or different, and are independently selected from substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

n is 0 to 3;

m is 0 to 5;

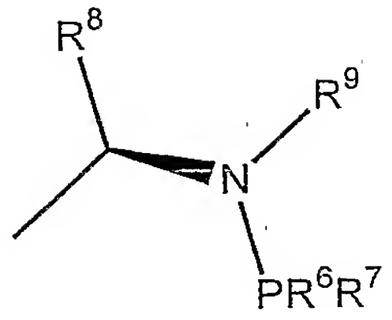
—Q is selected from:



wherein R^6 and R^7 are the same or different, and are independently selected from substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

R^8 is selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

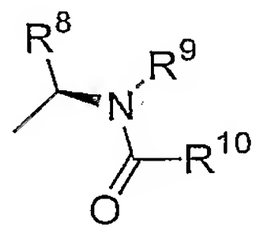
or —Q is selected from:



wherein R^6, R^7 and R^8 are, independently, as previously defined; and

R^9 is selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

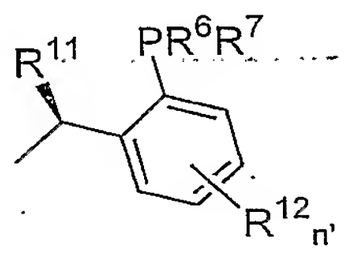
or —Q is selected from:



R^8 and R^9 are, independently, as previously defined; and

R^{10} is selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

or —Q is selected from:



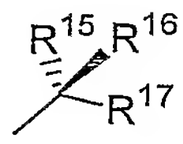
wherein R^6, R^7 are, as previously defined;

R^{11} is selected from OR^{13}, SR^{13}, NHR^{13}, $NR^{13}R^{14}$, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; wherein R^{13} and R^{14} are the same or different and are independently selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

R^{12} is selected from hydrogen, halogen, OR^{13}, SR^{13}, $NR^{13}R^{14}$, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; wherein R^{13}, R^{14} are, as previously defined; and

n' is 0 to 4;

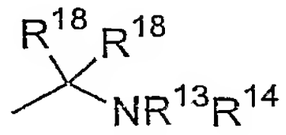
—R^5 is selected from:



wherein R^{15}, R^{16} and R^{17} are the same or different and are independently selected from hydrogen, OR^{13}, SR^{13}, $NR^{13}R^{14}$, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl,

substituted and unsubstituted alkenyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; wherein R^{13}, R^{14} are, as previously defined; or

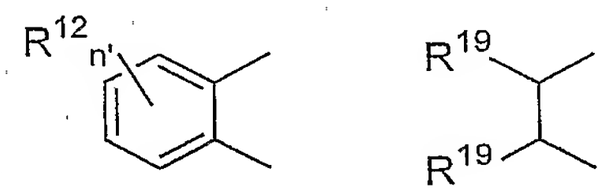
—R^5 is selected from:



wherein R^{13}, R^{14} are as previously defined; the two geminal substituents R^{18} together are a doubly bonded oxygen atom (i.e. $(R^{18})_2$ is =O), or each substituent R^{18} on its own is hydrogen;

G is selected from the group consisting of:

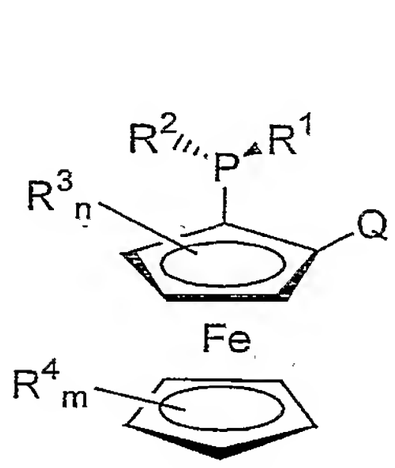
-CONH-R*-NHCO-, -CO-OR*O-CO-, -CO-R*CO-, -CH=N-R*-N=CH-, -CH_2NH-R*-NHCH_2-, -CH_2NHCO-R*-CONHCH_2-, -CH(R^8)NH-R*-NH(CH(R^8)-, -CH(R^8)NHCO-R*-CONHCH(R^8)-, -CONH-R-NHCO-, -CO-ORO-CO-, -CO-RCO-, -CH=N-R-N=CH-, -CH_2NH-R-NHCH_2-, -CH_2NHCO-R-CONHCH_2-, -CH(R^8)NH-R-NH(CH(R^8)-, -CH(R^8)NHCO-R-CONHCH(R^8)-; wherein R^8 is, independently, as previously defined; -R*- and –R- are selected from the group consisting of:



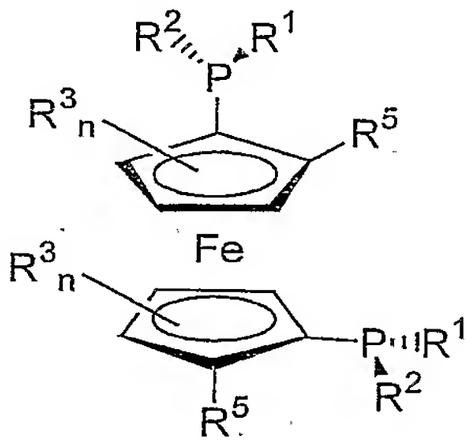
wherein R^{12} is as previously defined; R^{19} is selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted alkenyl, substituted and

unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; or $(R^{19})_2$ is $-(CH_2)_{m'}-$, n' is 0 to 4; and m' is 1 to 8;

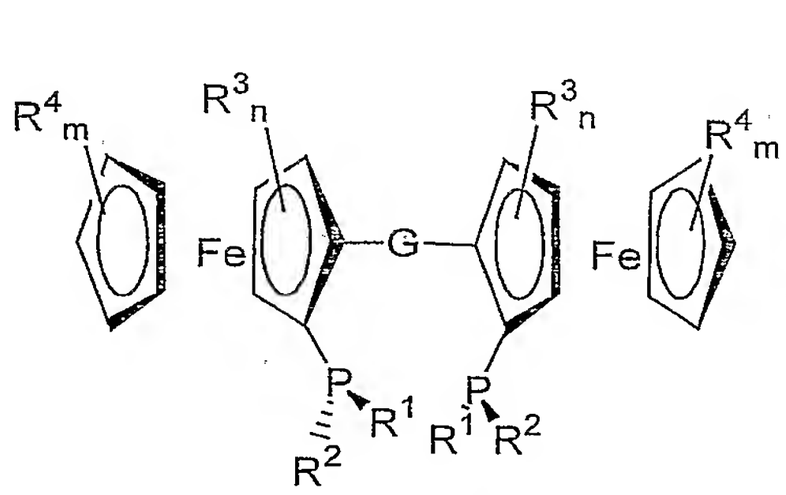
The invention also relates to the enantiomers (IV), (V) and (VI):



(IV)



(V)



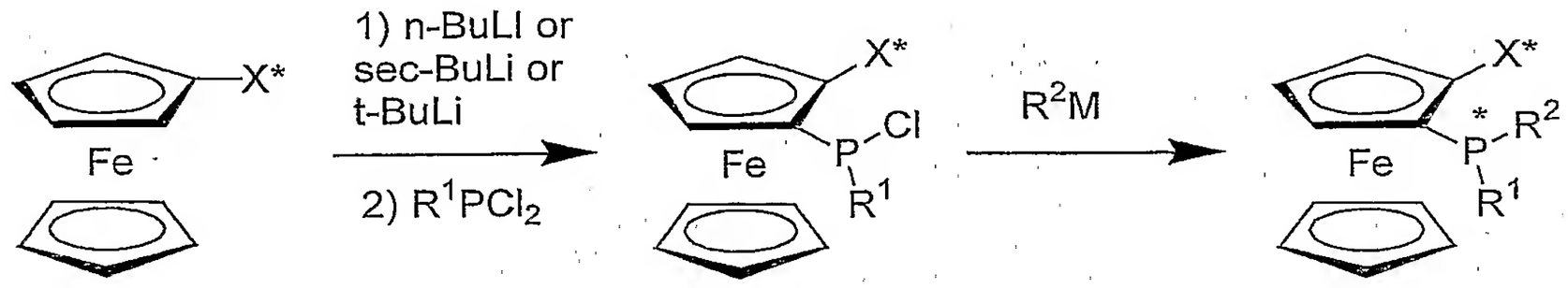
(VI)

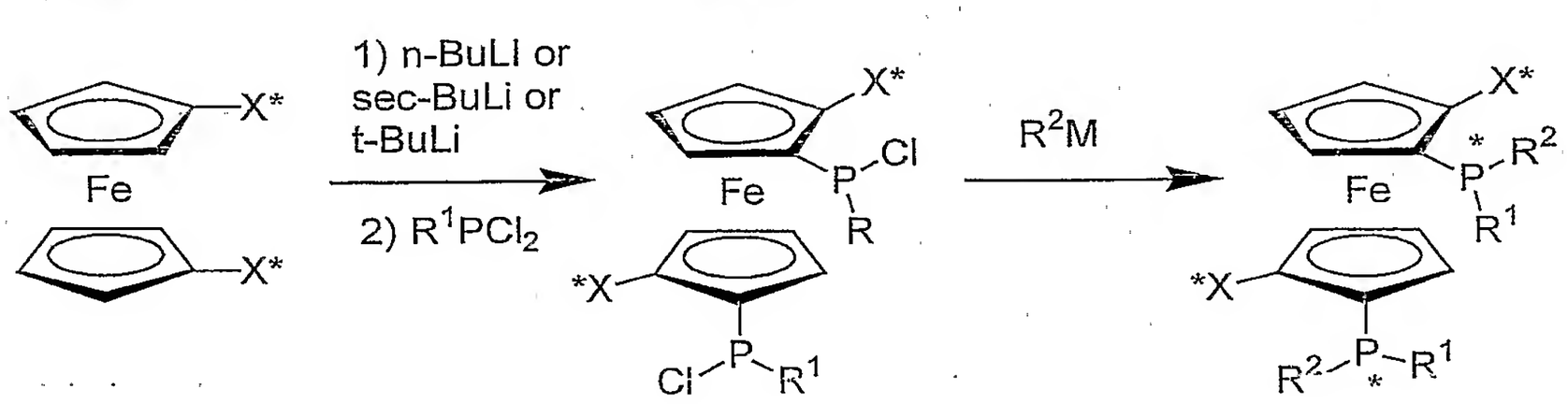
where the substituents are as defined in respect of Formulae (I), (II) and (III), with suitable changes in chirality where appropriate.

The introduction of phosphorus chirality may enhance the chiral discrimination produced by the catalyst when a matching among the planar chirality, carbon chirality and the chirality of phosphorus exists. Examples 30 to 34 below demostrate that a matching catalyst may give high ee and a mismatching one may give low ee).

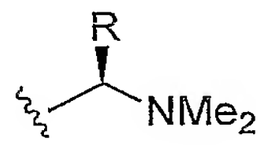
Also provided in accordance with the invention is a transition metal complex containing transition metal coordinated to the ligand of the invention. The metal is preferably a Group VIb or a Group VIII metal.

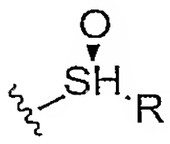
Synthesis of ferrocene-based phosphorus chiral phosphines may be effected with the use of a suitable chiral *ortho*-directing group:

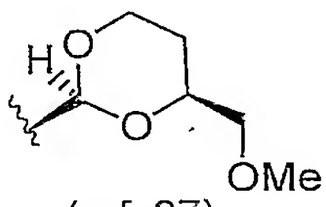


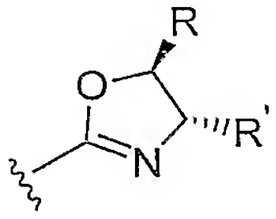


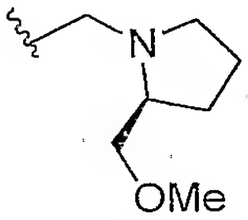
Chiral directing group:

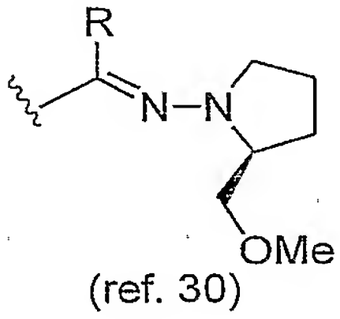
X* =  (ref. 25)

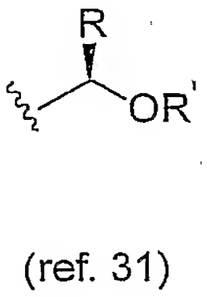
 (ref. 26)

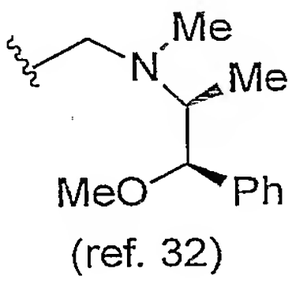
 (ref. 27)

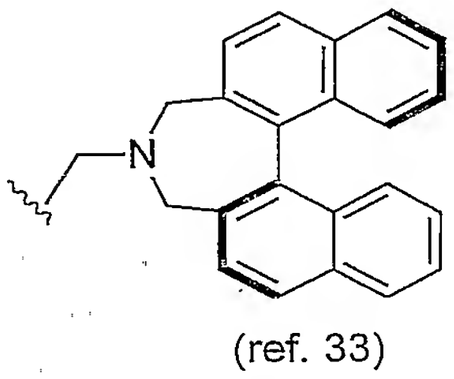
 (ref. 28)

 (ref. 29)

 (ref. 30)

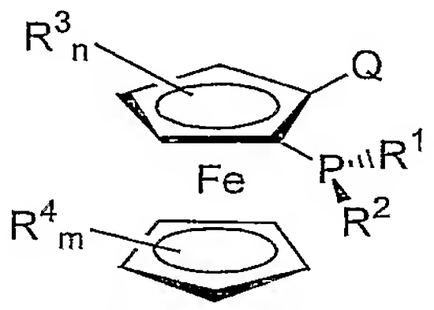
 (ref. 31)

 (ref. 32)

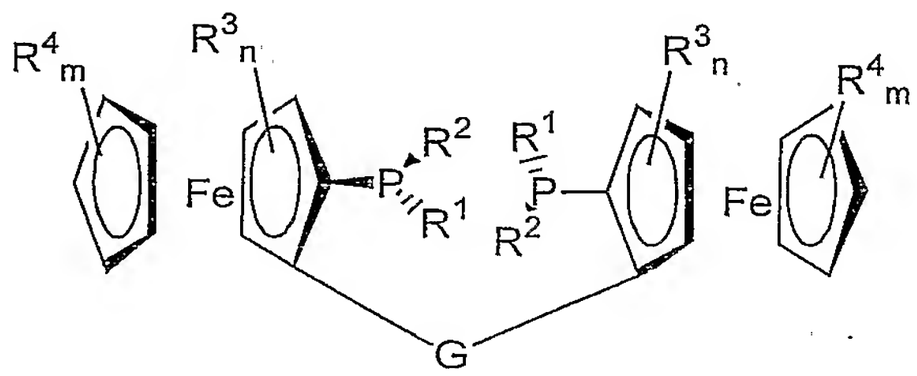
 (ref. 33)

Accordingly, the invention provides a method for preparing a phosphine ligand chiral at phosphorus comprising a ferrocene-based substrate having a chiral directing substituent on one or both rings, and subjecting the substituted ferrocene to an ortho-lithiation step before subsequently converting the ortho-lithiated substrate to a phosphine chiral at phosphorus.

Methods for the preparation of ligands having Formula (I) and (III) will now be more particularly described.



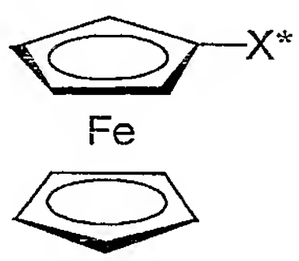
(I)



(III)

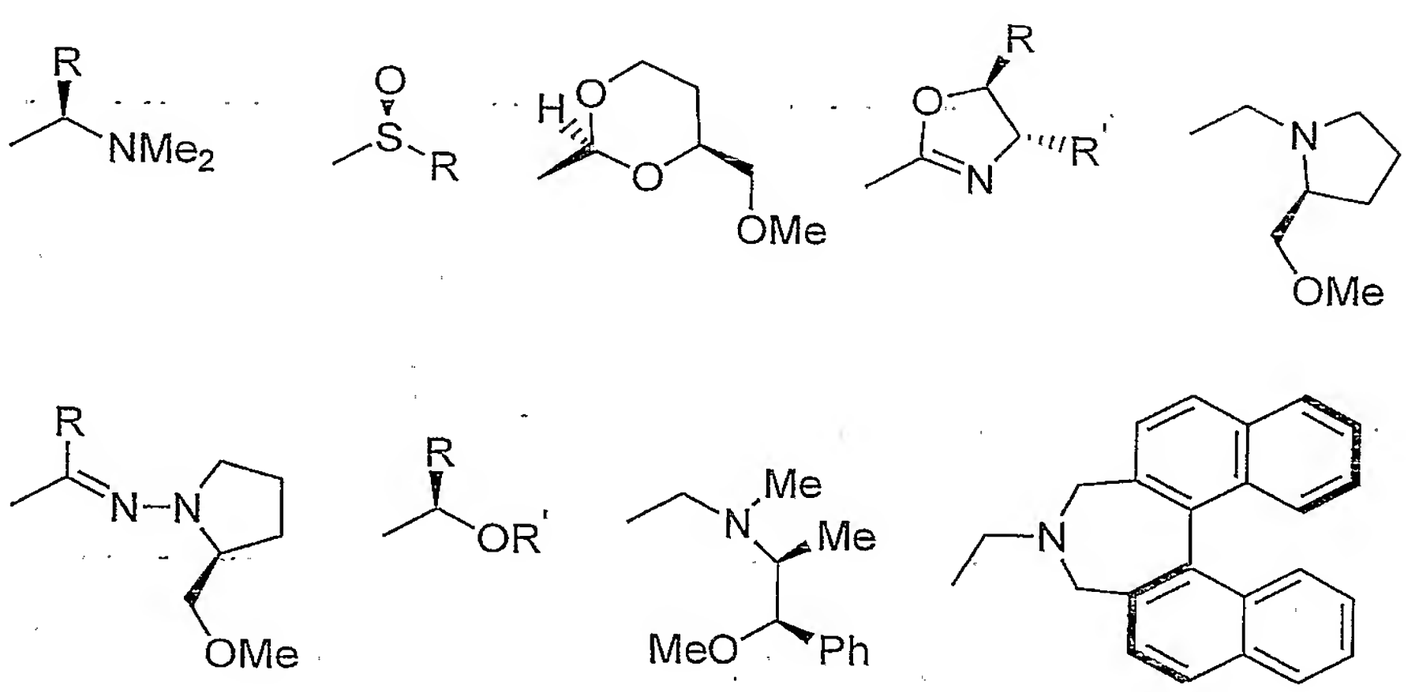
For example, one such method comprises the steps of :

subjecting a compound of the formula VII:

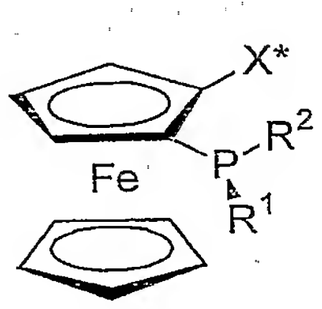


(VII)

wherein X* is chiral directing group, and is selected from the group consisting of :

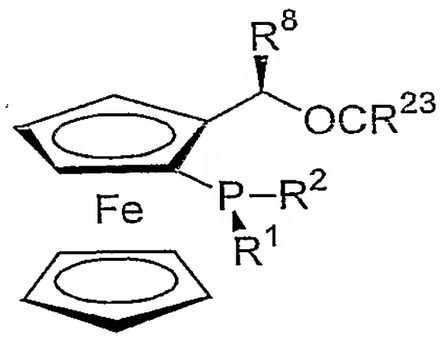


to mono-ortho-lithiation using n-butyllithium, sec-butyllithium or tert-butyllithium, and reacting the resulting monolithium compound *in situ* with a dichlorophosphine of the formula R^1PCl_2 followed by reacting with an organometallic reagent of the formula R^2M, wherein R^1 and R^2 are as defined above; M is Li or MgX wherein X is a halide, to obtain phosphorus chiral compound having formula VIII:

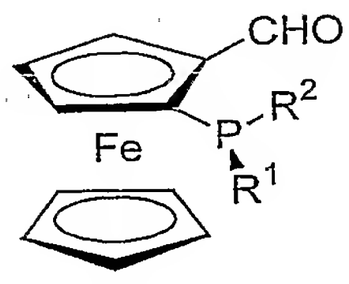


(VIII)

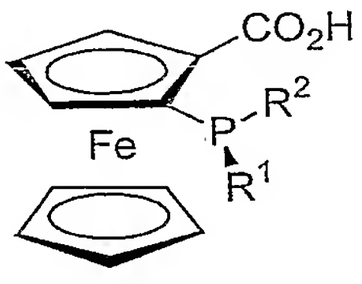
converting the compound having formula VIII to a compound having formula IX or X or XI:



(IX)

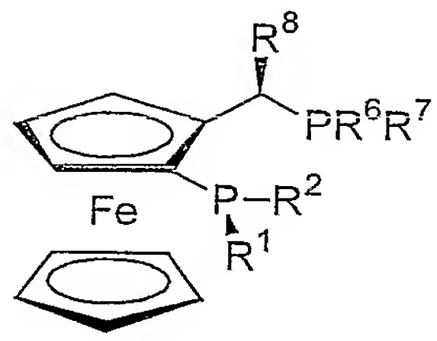


(X)



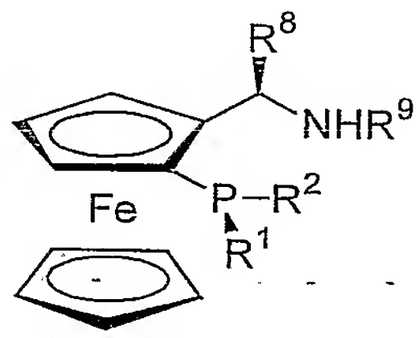
(XI)

reacting the compound having formula IX with a secondary phosphine of the formula R^6R^7PH wherein R^6, R^7 are, as previously defined, to obtain the diphosphine combining planar, phosphorus and carbon chirality having formula XII:



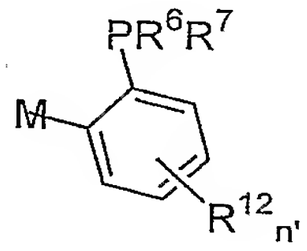
(XII)

reacting the compound having formula IX with an amine of the formula R^9NH_2 wherein R^9 is, as previously defined, to obtain the compound having formula XIII:



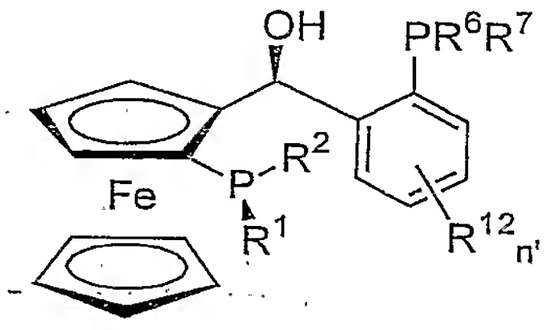
(XIII)

reacting the compound having formula IX with an amine of the formula XIV:



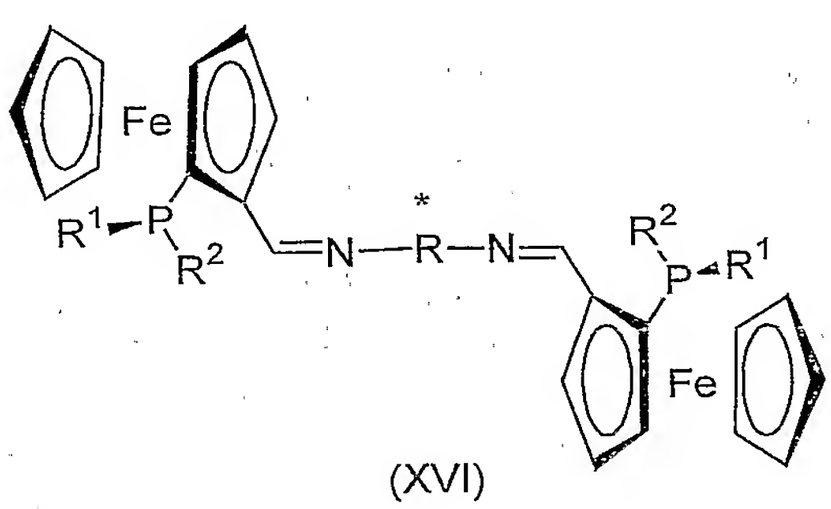
(XIV)

wherein R^6, R^7, R^{12} and n' are, as previously defined, and M is MgX or Li, to obtain the compound having formula XV:

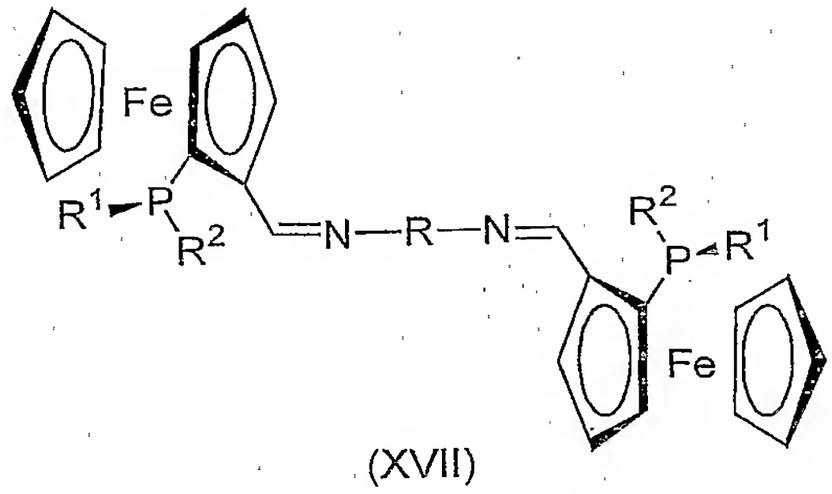


(XV)

reacting the compound having formula IX with an amine of the formula H_2N-R*-NH_2 or H_2N-R-NH_2 wherein R* and R are, as previously defined, to obtain the compound having formula XVI and XVII:

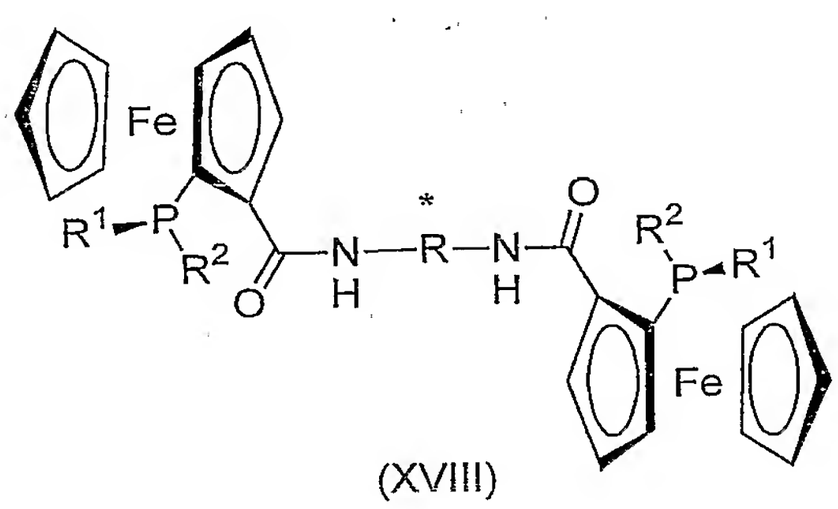


(XVI)

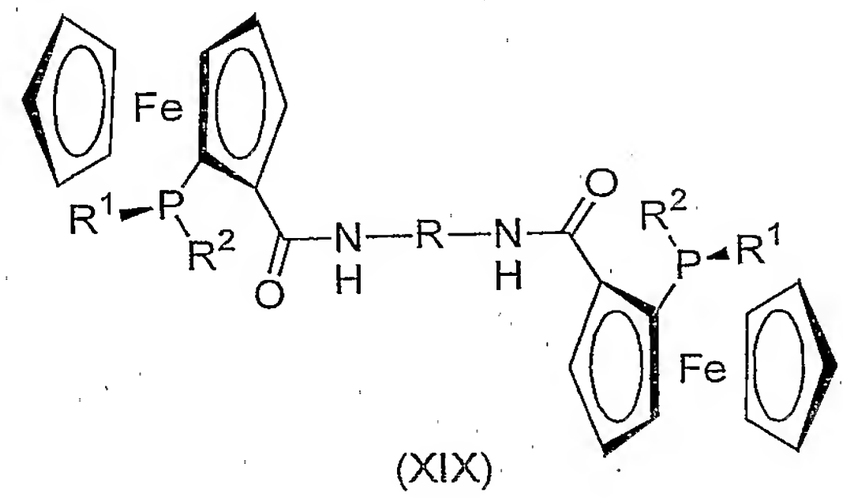


(XVII)

reacting the compound having formula X with an amine of the formula H_2N-R*-NH_2 or H_2N-R-NH_2 wherein R* and R are, as previously defined, to obtain the compound having formula XVIII and XIX:

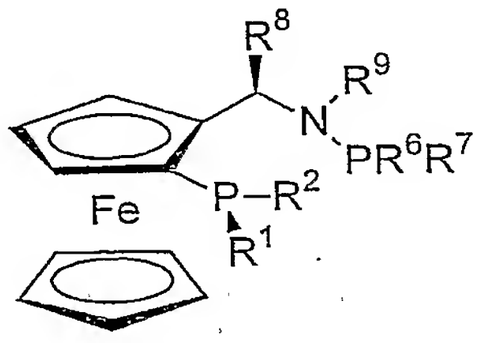


(XVIII)



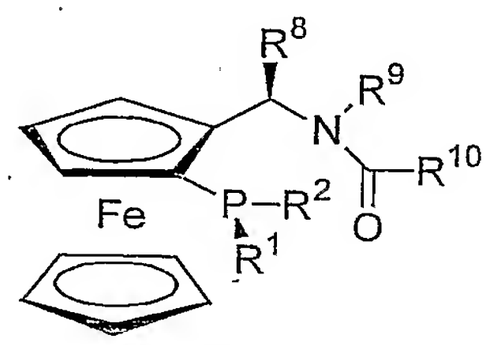
(XIX)

reacting the compound having formula XIII with a halophosphine of the formula R^6R^7PX wherein R^6, R^7 are, as previously defined, and X is chlorine, bromine and iodine, to obtain the compound having formula XX:



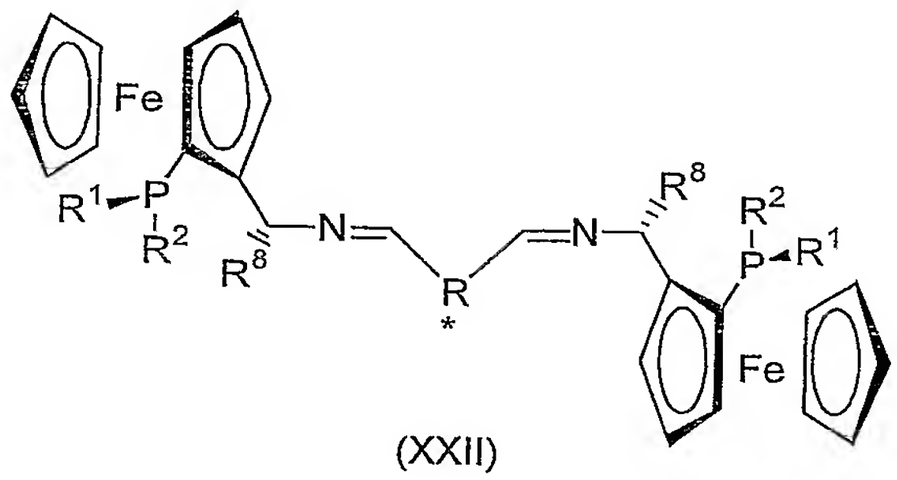
(XX)

reacting the compound having formula XIII with an acid derivative of the formula $R^{10}COY$ wherein R^{10} is, as previously defined, and Y is a halide, a sulfate, an imidazole, $R^{10}COO$- or hydrogen, to obtain the compound having formula XXI:

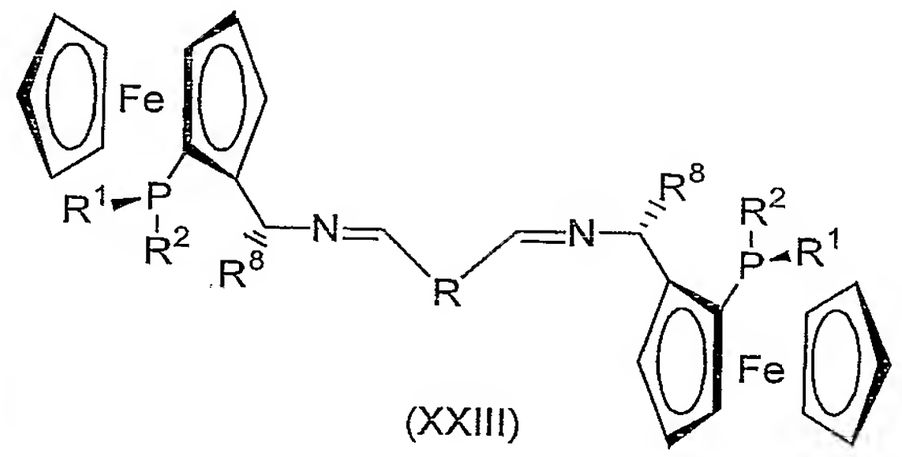


(XXI)

reacting the compound having formula XIII with an aldehyde of the formula OHC-R*-CHO or OHC-R-CHO wherein R^9 is hydrogen, and R* and R are, as previously defined, to obtain the compound having formula XXII and XXIII:

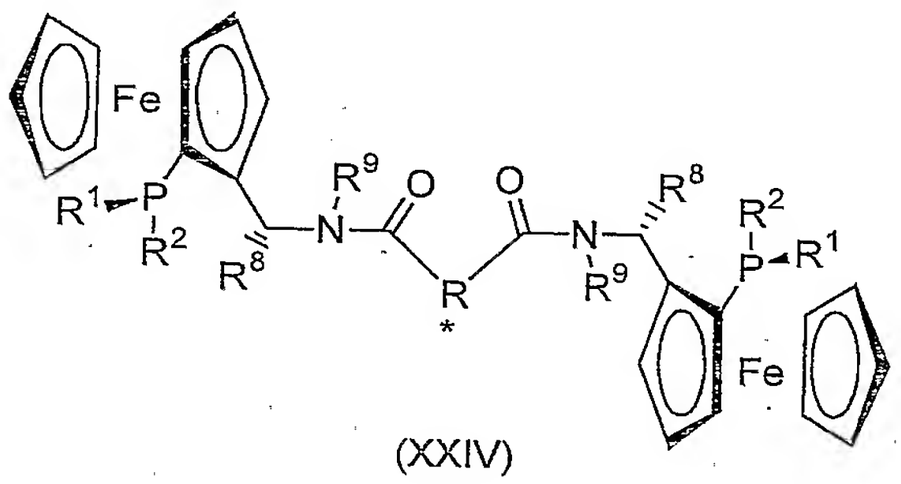


(XXII)

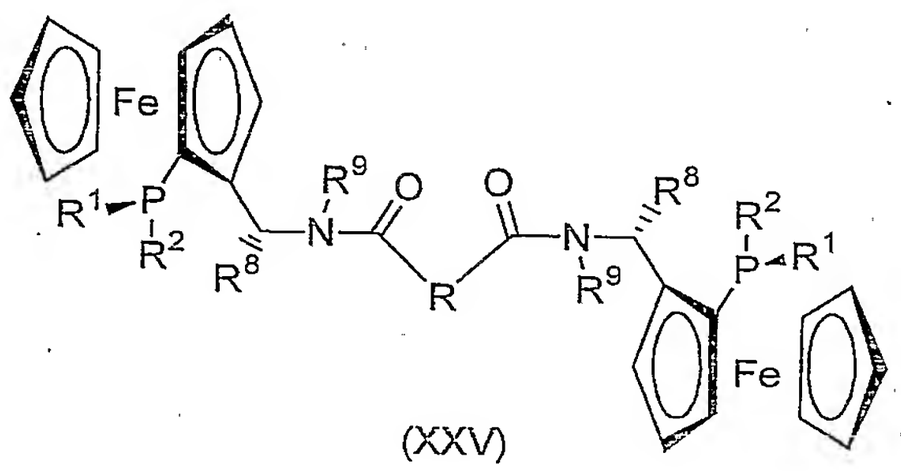


(XXIII)

reacting the compound having formula XIII with an acid derivative of the formula YOC-R*-COY and YOC-R-COY wherein R*, R and Y are, as previously defined, to obtain the compound having formula XXIV and XXV:

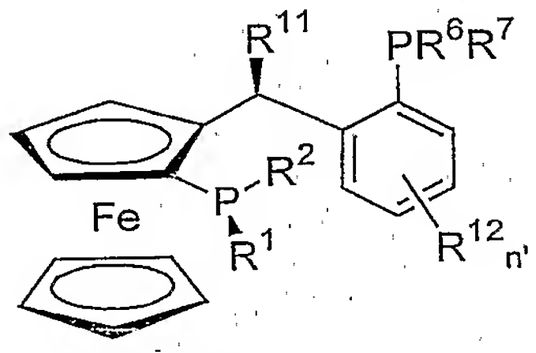


(XXIV)



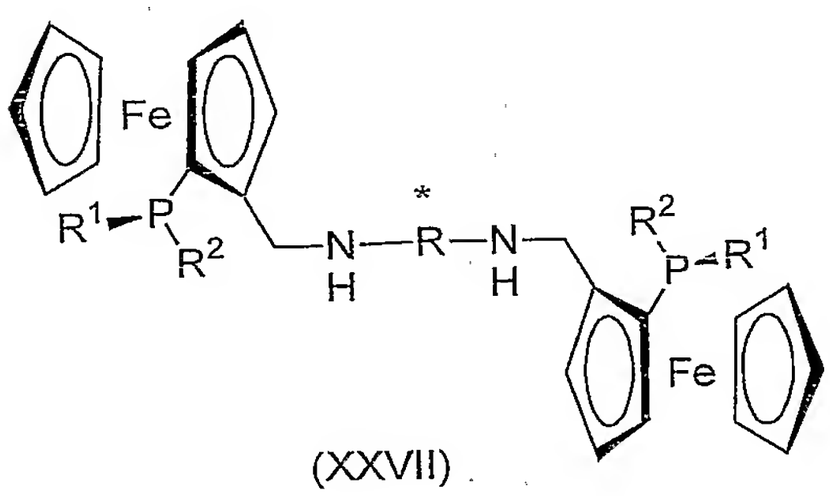
(XXV)

converting the compound having formula XV into the compound having formula XXVI:

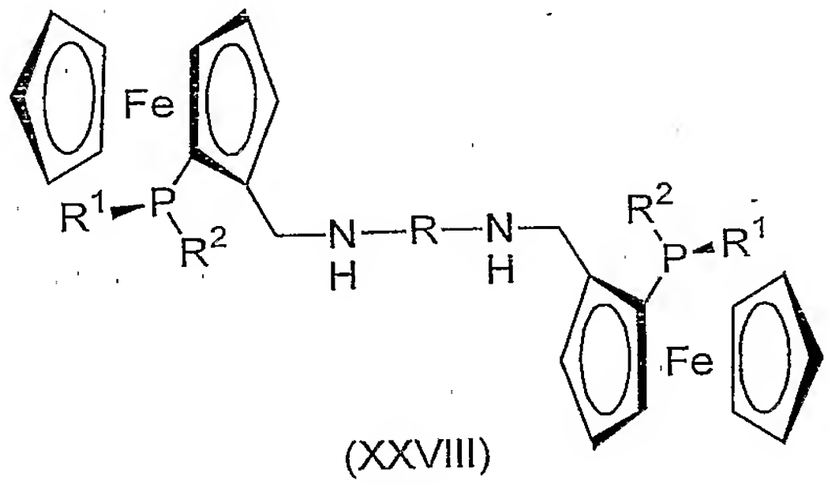


(XXVI)

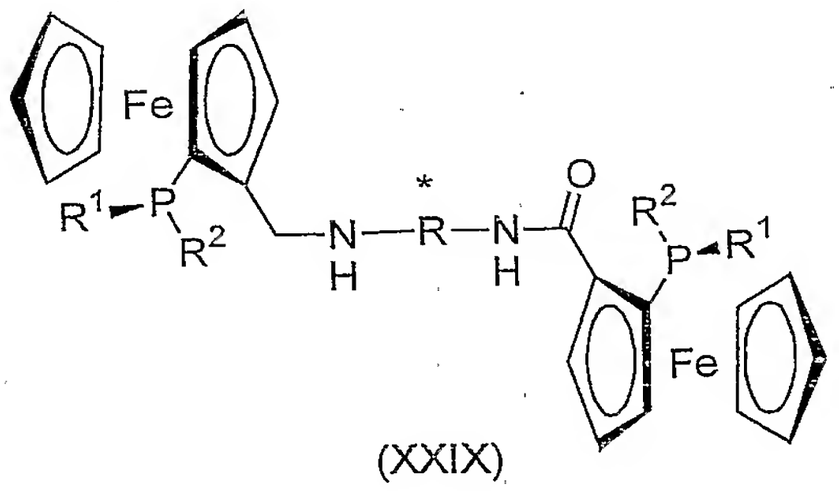
reducing the compound having formula XVI, XVII, XVIII, XIX, XXII, XXIII, XXIV, XXV to obtain the compound having formula XXVII, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII, XXXIV:



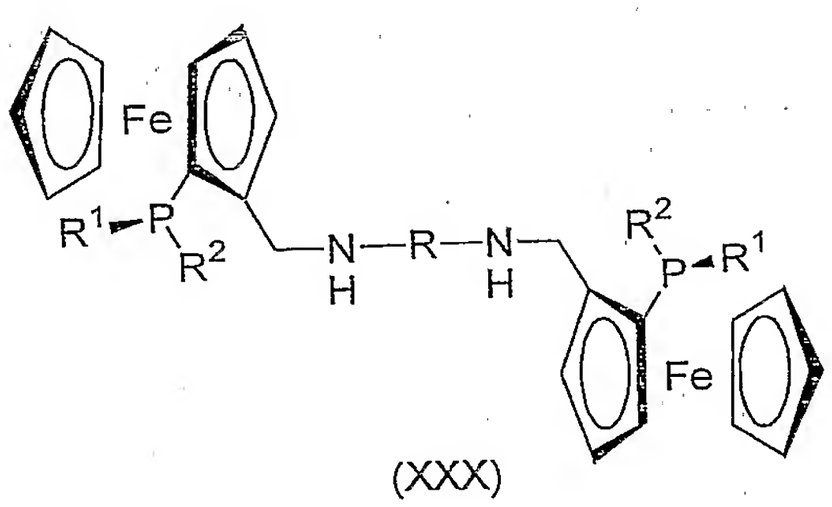
(XXVII)



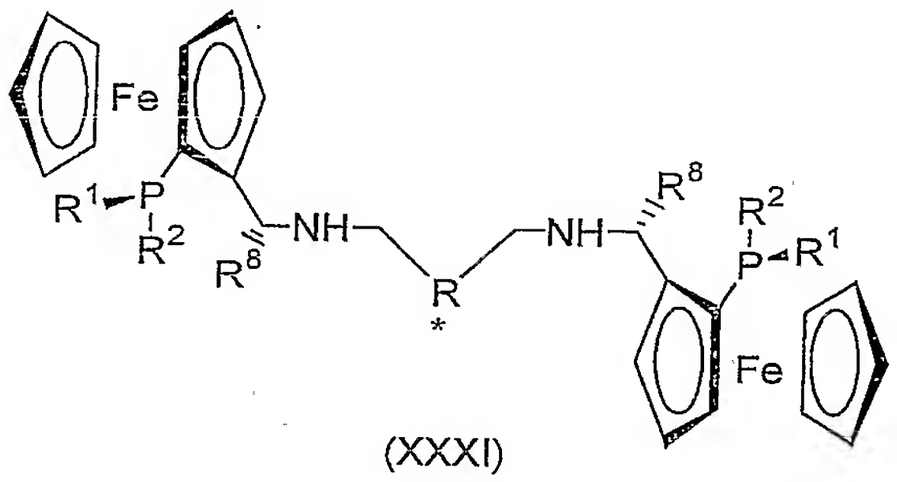
(XXVIII)



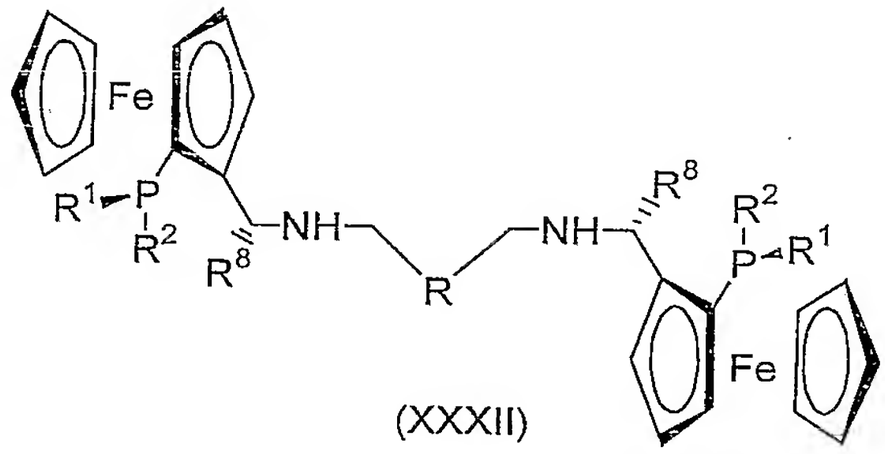
(XXIX)



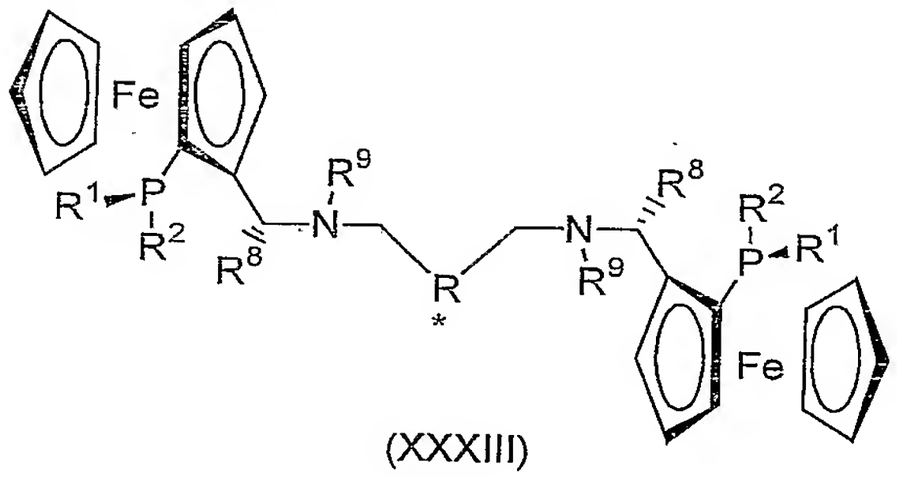
(XXX)



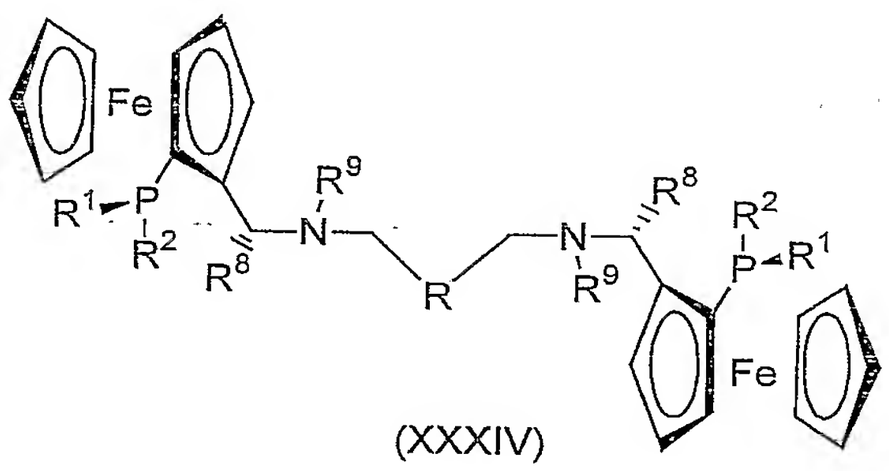
(XXXI)



(XXXII)

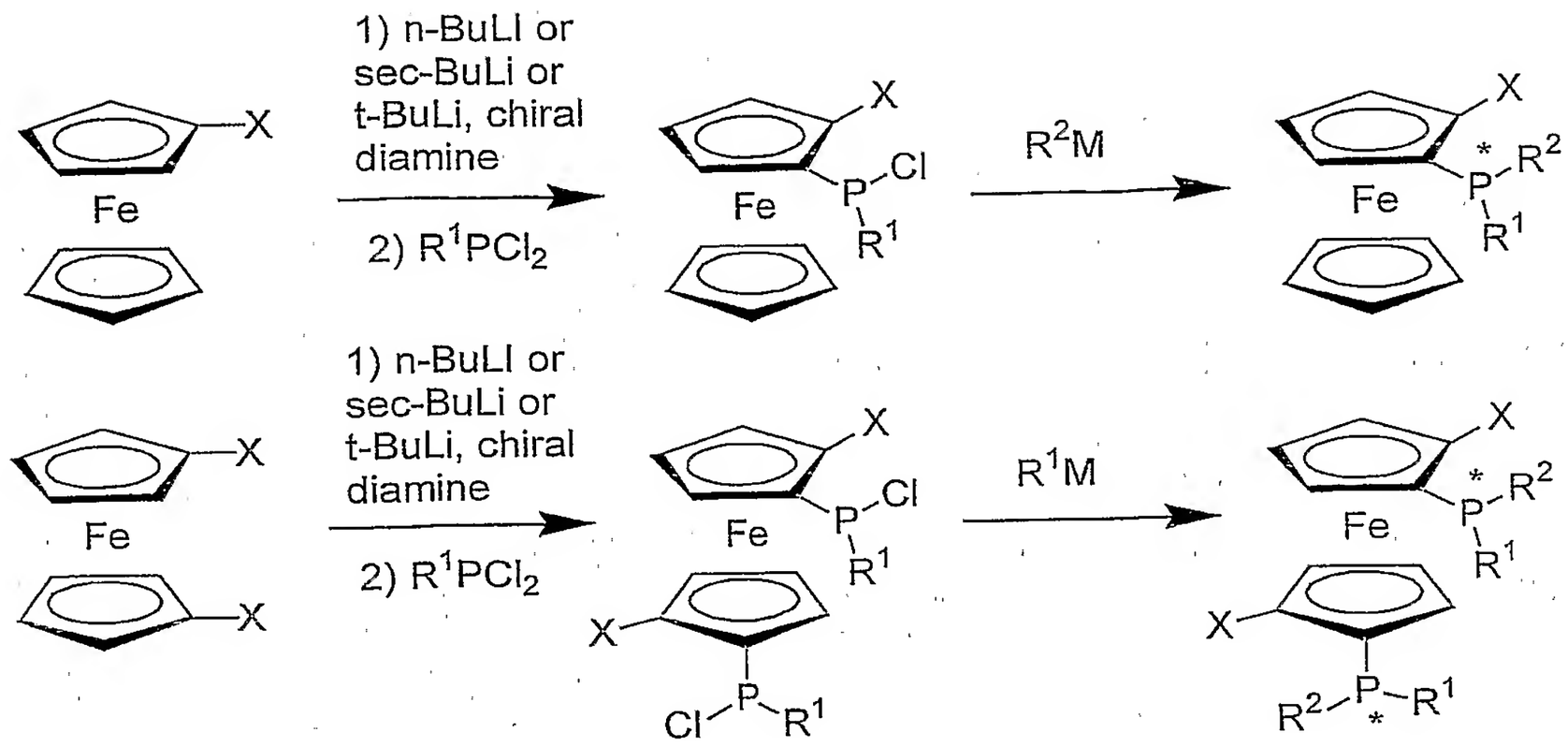


(XXXIII)

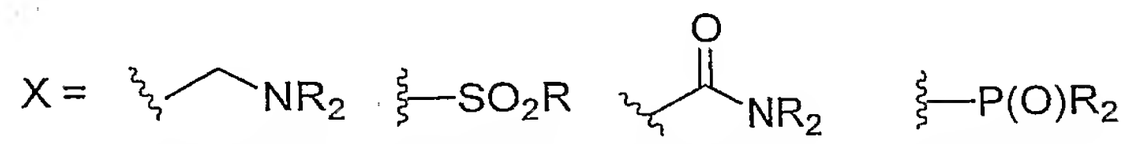


(XXXIV)

Synthesis of ferrocene-based phosphines chiral at phosphorus may be also effected with the use of enantioselective ortho-lithiation:

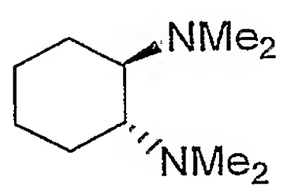


Achiral directing group:

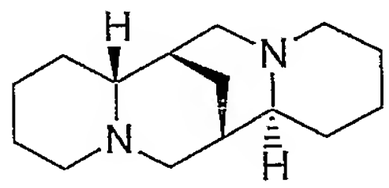


(ref. 34) (ref. 34) (ref. 35) (ref. 36)

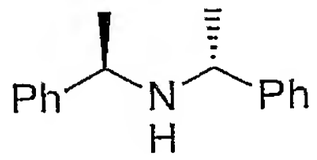
Chiral diamine:



(ref. 34)



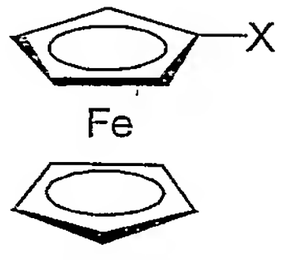
(ref. 35)



(ref. 36)

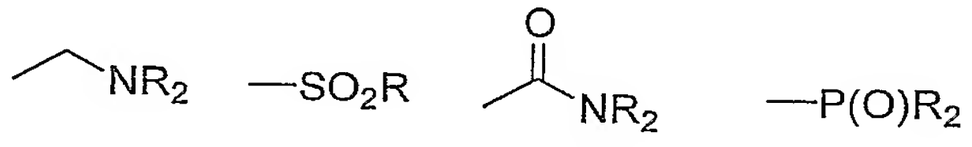
Accordingly, the invention provides a method for preparing a chiral diphosphine ligand comprising a ferrocene-based substrate having an achiral directing substituent on one or both rings, and subjecting the substituted ferrocene to an enantioselective ortho-lithiation step before subsequently converting the ortho-lithiated substrate to phosphorus chiral phosphines.

Thus, one method according to the present invention for preparing the ligand of Formula (I) or (III) comprises providing a compound of the formula XXXVII:

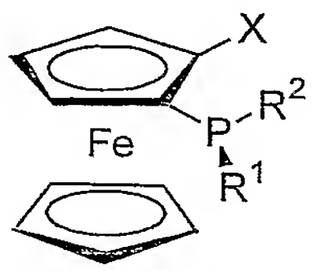


(XXXVII)

wherein X is a chiral directing group, and is selected from:



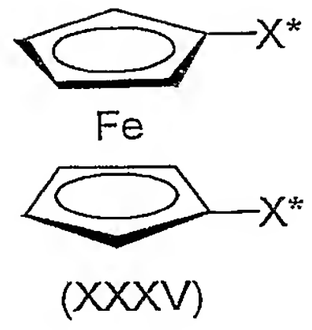
and subjecting the compound to enantioselective mono-ortho-lithiation using n-butyllithium or sec-butyllithium or tert- butyllithium in the presence of a homochiral tertiary amine, and reacting the resulting chiral monolithium compound *in situ* with a dichlorophosphine of the formula R^1PCl_2 followed by reacting with an organometallic reagent of the formula R^2M, wherein R^1 and R^2 are as defined hereinabove; M is Li or MgX wherein X is a halide, to obtain phosphorus chiral compound having formula XXXVIII:



(XXXVIII)

and converting the compound having formula XXXVIII to a compound having Formula (I) or(III).

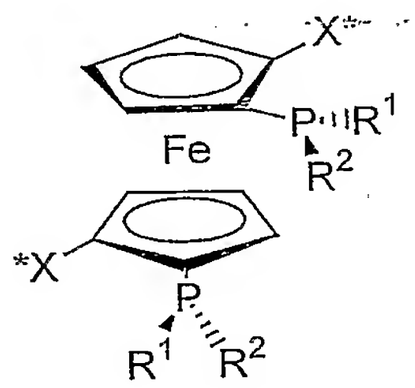
One method according to the invention for preparing the ligand of Formula (II) comprises providing a compound of the Formula XXXV:



(XXXV)

wherein X* is as previously defined; and subjecting the compound to bis-ortho-lithiation using n-butyllithium, sec-butyllithium or tert- butyllithium, and reacting the resulting bislithium compound *in situ* with a dichlorophosphine of the formula R^1PCl_2 followed by reacting with an organometallic reagent of the formula R^2M,

wherein R^1 and R^2 are as defined in claim 3; M is Li or MgX wherein X is a halide, to obtain a phosphorus chiral compound having formula XXXVI:



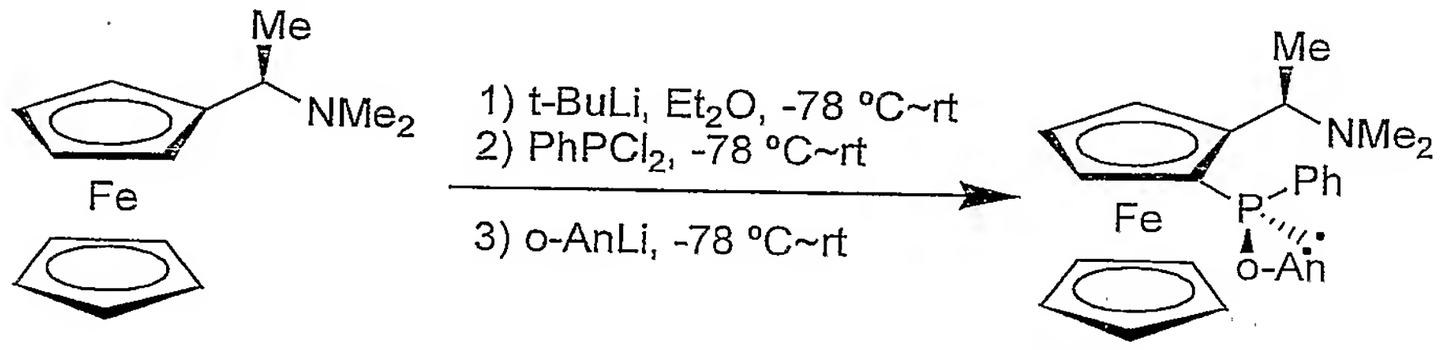
(XXXVI)

and converting the compound having formula XXXVI to a compound having formula (II).

The invention will now be more particularly illustrated with reference to the following Examples.

Example 1

(R_C, S_{Fe}, S_P)-2-[(1-N,N-Dimethylamino)ethyl]-1-[(2-methoxyphenyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-2]:



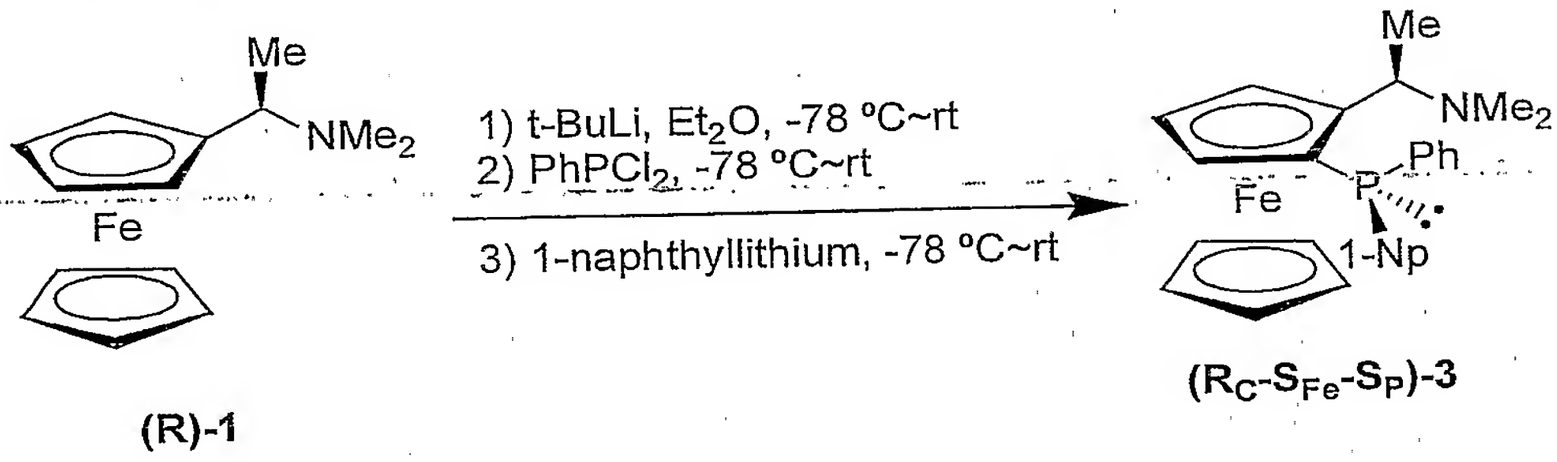
(R)-1 **R_C-S_{Fe}-S_P-2**

To a solution of (R)-N,N-dimethyl-1-ferrocenylethylamine [(R)-Ugi's amine, (R)-1] (3.86 g, 15 mmol) in Et_2O (50 mL) was added 1.7 M t-BuLi solution in pentane (9.7 mL, 16.5 mmol) over 10 min via a syringe at –78 °C. After addition was completed, the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The resulting red solution was cooled to –78 °C again, and dichlorophenylphosphine (2.24 mL, 16.5 mmol) was added in one portion. After stirring for 10 min at –78 °C, the mixture was slowly warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then cooled to –78 °C again, and a solution of (2-methoxy)phenyllithium [prepared from 2-bromoanisole (3.32 g, 17.7 mmol) and 1.7 M t-BuLi solution in pentane (20.8 mL, 35.4 mmol) in Et_2O (90 mL) at –78 °C] was added slowly via a cannula. The mixture was warmed to room temperature overnight, and filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc-Et3N = 85:10:5) to afford the title compound (6.50 g, 92%) as orange crystals. ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.29 (d, 3H, *J* = 6.5 Hz); 1.80 (s, 6H); 3.91 (s, 3H); 3.97 (s, 6H, overlap); 4.11 (m, 1H), 4.25 (t, 1H, *J* = 2.2 Hz); 4.37 (br. s, 1H); 6.87 (m, 1H); 6.94 (dd, 1H, *J* =

8.3 and 6.7 Hz); 7.12 ~ 7.23 (m, 6H); 7.31 (m, 1H); ^{31}P NMR ($CDCl_3$, 162 MHz): δ –38.82. The absolute configuration of (R_C, S_{Fe}, S_P)-**2** was determined by single-crystal X-ray diffraction analysis.

Example 2

(R_C, S_{Fe}, S_P)-2-[(1-N,N-Dimethylamino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-3]:



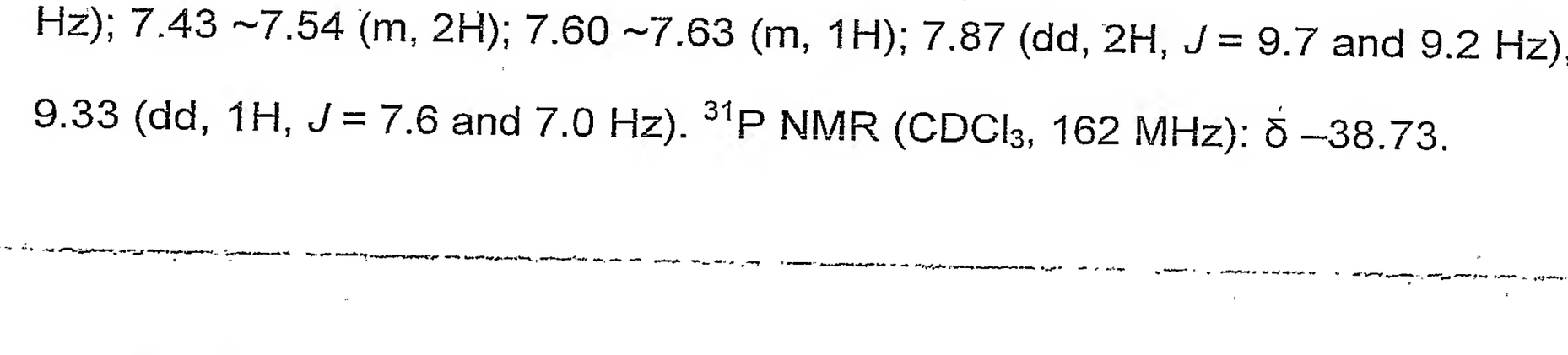
(R)-1 **(R_C-S_{Fe}-S_P)-3**

To a solution of (R)-N,N-dimethyl-1-ferrocenylethylamine [(R)-Ugi's amine, (R)-1] (5.15 g, 20 mmol) in Et_2O (60 mL) was added 1.7 M t-BuLi solution in pentane (12.94 mL, 22 mmol) over 10 min via a syringe at –78 °C. After addition was completed, the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The resulting red solution was cooled to –78 °C again, and dichlorophenylphosphine (2.99 mL, 22 mmol) was added in one portion. After stirring for 10 min at –78 °C, the mixture was slowly warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then cooled to –78 °C again, and a solution of 1-naphthyllithium [prepared from 1-bromonaphthalene (5.38 g, 26 mmol) and 1.7 M t-BuLi solution in pentane

(30.6 mL, 52 mmol) in Et_2O (120 mL) at –78 °C] was added slowly via a cannula. The mixture was warmed to room temperature overnight, and filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc-Et_3N = 90:6:4) to afford the title compound (8.75 g, 89%) as orange crystals. ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.33 (d, 3H, J = 6.8 Hz); 1.91 (s, 6H); 3.59 (s, 5H); 4.00 (m, 1H); 4.17 (m, 1H); 4.26 (t, 1H, J = 2.2 Hz); 4.38 (m, 1H); 7.13 ~ 7.2 (m, 5H); 7.39 (t, 1H, J = 6.7 Hz); 7.43 ~7.54 (m, 2H); 7.60 ~7.63 (m, 1H); 7.87 (dd, 2H, J = 9.7 and 9.2 Hz), 9.33 (dd, 1H, J = 7.6 and 7.0 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz): δ –38.73.

Example 3

(R_C, S_{Fe}, S_P)-2-[(1-N,N-Dimethylamino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-3] and (R_C, S_{Fe}, R_P)-2-[(1-N,N-Dimethylamino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, R_P)-4]:



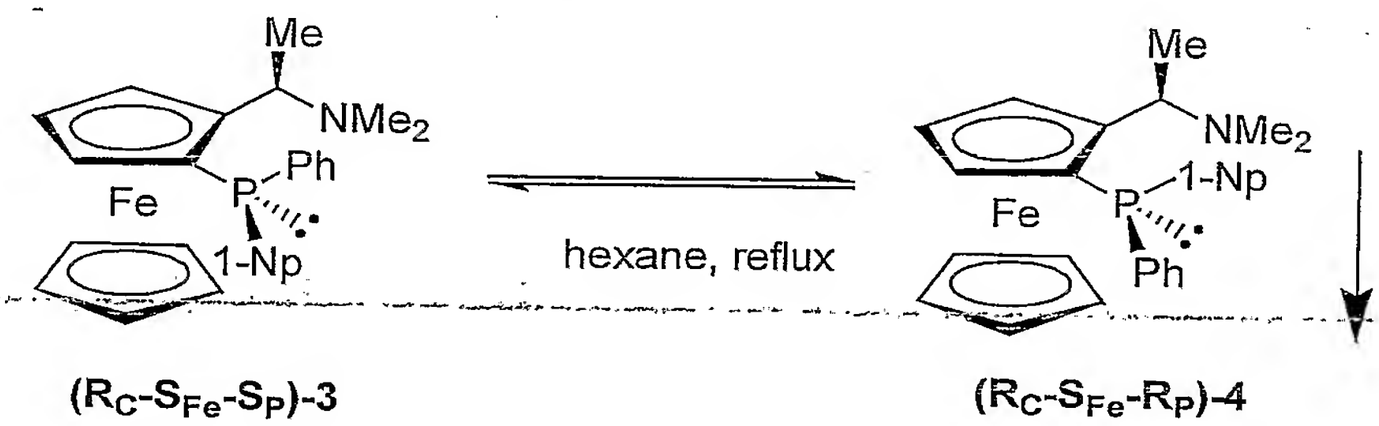
(R)-1 (R_C-S_{Fe}-S_P)-3 (R_C-S_{Fe}-R_P)-4

To a solution of (R)-N,N-dimethyl-1-ferrocenylethylamine [(R)-Ugi's amine, (R)-1] (1.29 g, 5 mmol) in Et_2O (15 mL) was added 1.7 M t-BuLi solution in pentane (3.2 mL, 5.5 mmol) over 10 min via a syringe at –78 °C. After addition was completed, the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The resulting red solution was cooled to –78 °C again, and dichlorophenylphosphine (0.75 mL, 5.5 mmol) was added in one portion. After stirring for 10 min at –78 °C, the mixture was slowly warmed to room temperature, and stirred for 1.5 h at room temperature. Then to the mixture a solution of 1-naphthyllithium [prepared from 1-bromonaphthalene (1.35 g, 6.5 mmol) and 1.7 M t-BuLi solution in pentane (7.6 mL, 13 mmol) in Et_2O (30 mL) at –78 °C] was added via a cannula at room temperature. The mixture was stirred overnight at room temperature and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by chromatography (SiO_2, hexane-EtOAc-Et3N = 85:10:5) to afford the title compound (2.21 g, 90%) as a mixture of two isomers. The ratio of (R_c, S_{Fe}, S_P)-**3** to (R_c, S_{Fe}, R_P)-**4** is about 5:1. As (R_c, S_{Fe}, R_P)-**4** is insoluble in cold hexane and (R_c, S_{Fe}, S_P)-**3** is very soluble in cold hexane, the two isomers can be easily separated by crystallization from hexane. (R_c, S_{Fe}, R_P)-**4** : ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.25 (d, 3H, *J* = 6.8 Hz); 1.60 (s, 6H); 3.88 (br. s, 1H); 4.00 (s, 5H); 4.16 (m, 1H), 4.29 (t, 1H, *J* = 2.2 Hz); 4.42 (br. s, , 1H); 7.16 ~ 7.19 (m, 1H); 7.28 ~ 7.29 (m, 5H), 7.32 ~ 7.35 (m, 1H); 7.59 ~ 7.63 (m, 2H); 7.69 (d, *J* = 8.2 Hz); 7.76 (d, *J* = 7.6 Hz); 8.45 (m, 1H). ^{31}P NMR ($CDCl_3$, 162 MHz): δ –31.36. The absolute

configuration of (R_C, S_{Fe}, R_P)-**4** was determined by single-crystal X-ray diffraction analysis.

Example 4

(R_C, S_{Fe}, R_P)-2-[(1-N,N-Dimethylamino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, R_P)-4]:

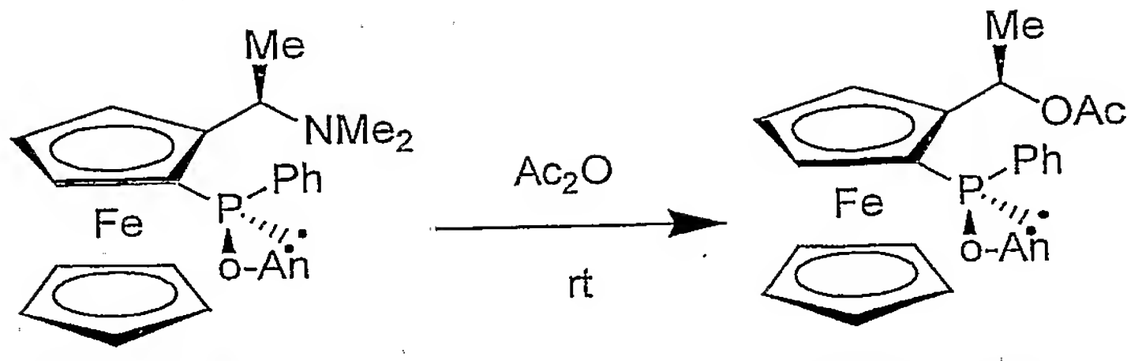


(R_C-S_{Fe}-S_P)-3 **(R_C-S_{Fe}-R_P)-4**

A solution of (R_C, S_{Fe}, S_P)-**3** (491 mg, 1.0 mmol) in hexane (5 mL) was refluxed overnight. After cooling to room temperature, the precipitate was filtered and washed with cold hexane to give the pure (R_C, S_{Fe}, R_P)-**4**.

Example 5

(R_C, S_{Fe}, S_P)-2-(1-Acetoxyethyl)-1-[(2-methoxyphenyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-5]:

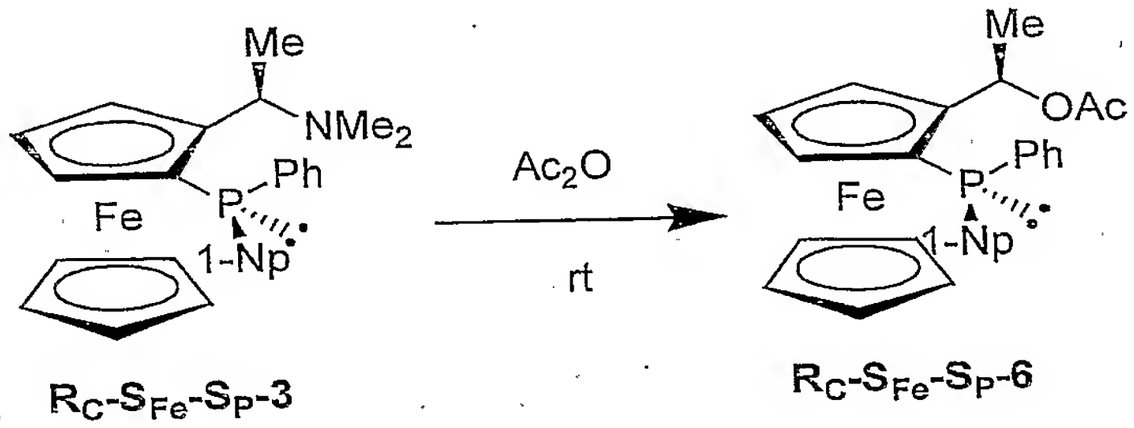


R_C-S_{Fe}-S_P-2 R_C-S_{Fe}-S_P-5

A solution of (R_c, S_{Fe}, S_P)-**2** (1.18 g, 2.5 mmol) in acetic anhydride (10 mL) was stirred for 60 h at room temperature. The excess acetic anhydride was removed under reduced pressure (<1 Torr, <30 °C) to give the title compound (1.21 g, 100%) as yellow solid, which is pure enough for the use in the next reaction. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.19 (s, 3H); 1.64 (d, 3H, J = 6.5 Hz); 3.90 (s, 3H); 3.92 (m, 1H); 4.07 (s, 5H); 4.34 (t, 1H, J = 2.6 Hz); 5.55 (m, 1H);6.15 (m, 1H); 6.87 (td, 1H, J = 7.4 and 0.9 Hz); 6.95 (q, 1H, J = 4.8 Hz); 7.08 ~ 7.21 (m, 6H); 7.35 (m, 1H); ^{31}P NMR ($CDCl_3$, 162 MHz): δ –39.30.

Example 6

(R_c, S_{Fe}, S_P)-2-(1-Acetoxyethyl)-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_c, S_{Fe}, S_P)-6]:

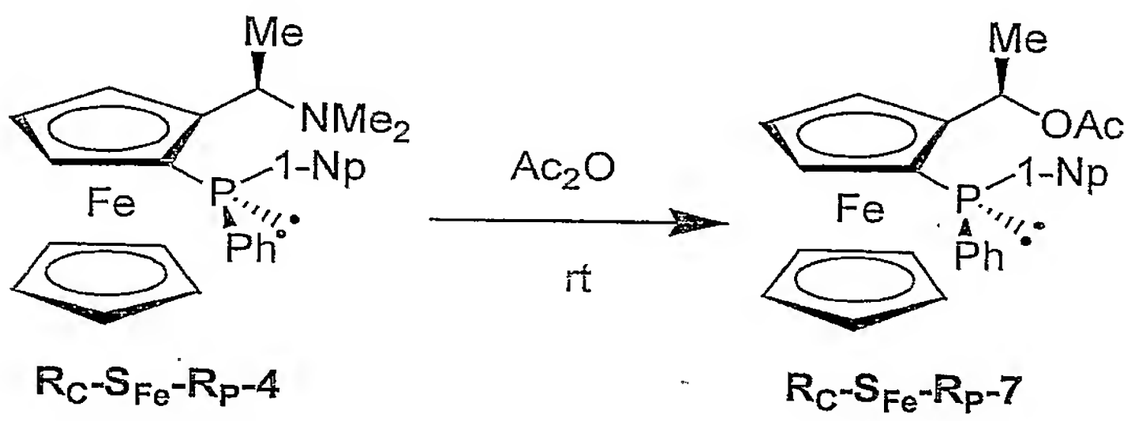


R_C-S_{Fe}-S_P-3 R_C-S_{Fe}-S_P-6

A solution of (R_C, S_{Fe}, S_P)-**3** (1.47 g, 3.0 mmol) in acetic anhydride (20 mL) was stirred for 60 h at room temperature. The excess acetic anhydride was removed under reduced pressure (<1 Torr, <30 °C) to give the title compound (1.52 g, 100%) as yellow solid, which is pure enough for the use in the next reaction. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.29 (s, 3H); 1.67 (d, 3H, *J* = 6.5 Hz); 3.72 (s, 3H); 3.94 (m, 1H); 4.07 (s, 5H); 4.35 (t, 1H, *J* = 2.6 Hz); 5.57 (m, 1H); 6.28 (m, 1H); 7.13 ~ 7.22 (m, 5H); 7.89 (t, 2H, *J* = 7.0 Hz); 9.28 (t, 1H, *J* = 7.0 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ –39.81.

Example 7

(R_C, S_{Fe}, R_P)-2-(1-Acetoxyethyl)-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, R_P)-7]:

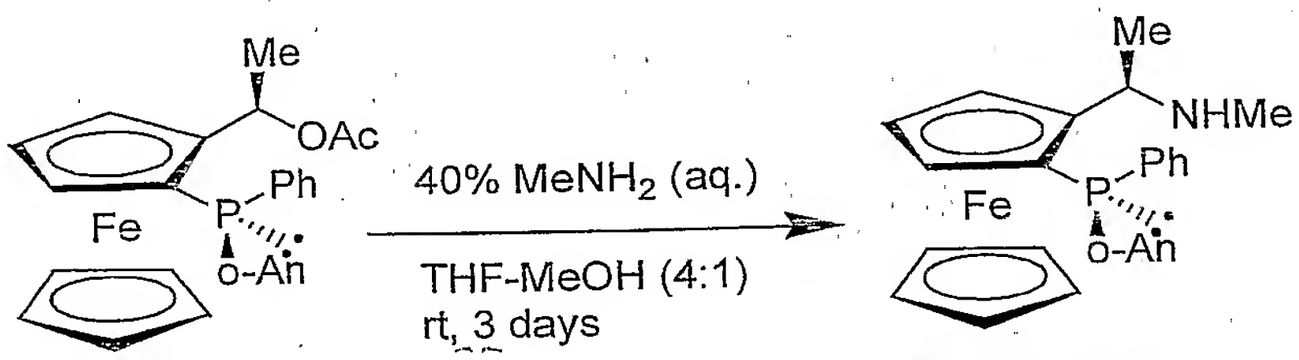


R_C-S_{Fe}-R_P-4 R_C-S_{Fe}-R_P-7

A solution of (R_C, S_{Fe}, S_P)-**4** (1.47 g, 3.0 mmol) in acetic anhydride (20 mL) was stirred for 60 h at room temperature. The excess acetic anhydride was removed under reduced pressure (<1 Torr, <30 °C) to give the title compound (1.52 g, 100%) as yellow solid, which is pure enough for the use in the next reaction.

Example 8

(R_C, S_{Fe}, S_P)-2-[(1- N-Methylamino)ethyl]-1-[(2-methoxyphenyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-8]:

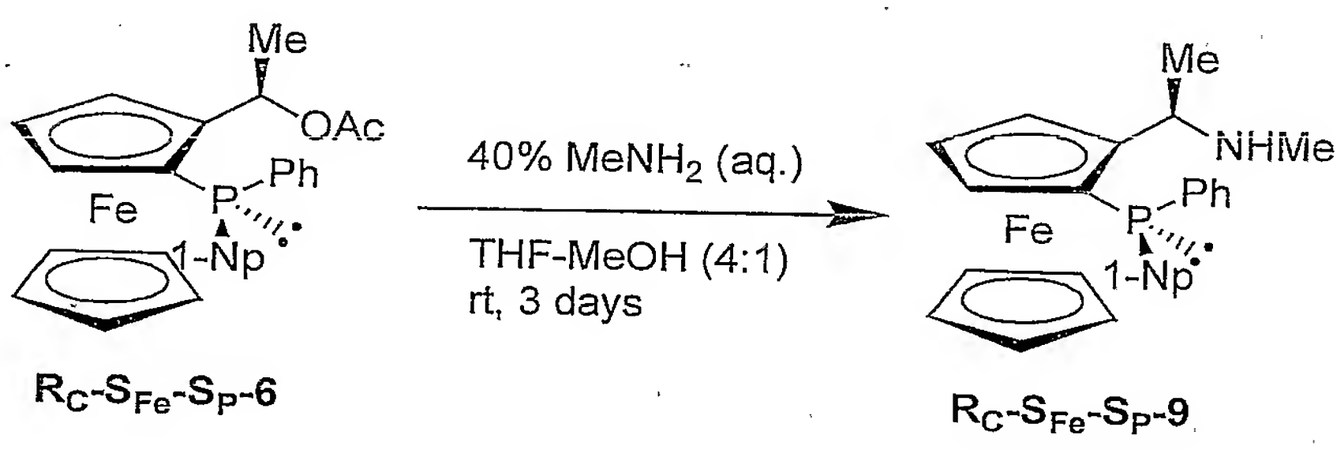


R_C-S_{Fe}-S_P-5 R_C-S_{Fe}-S_P-8

A solution of (R_C, S_{Fe}, S_P)-**5** (1.21 g, 2.5 mmol) and 40% methylamine aqueous solution (6.0 mL) in THF (20 mL) and MeOH (5 mL) was stirred for 3 days at room temperature, and concentrated. The residue was dissolved in Et2O (20 mL), washed with brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by chromatography (SiO2, hexane-EtOAc-Et3N = 80:15:5) to give the title compound (1.07 g, 94%) as orange crystals.

Example 9

(R_C, S_{Fe}, S_P)-2-[(1- N-Methylamino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-9]:

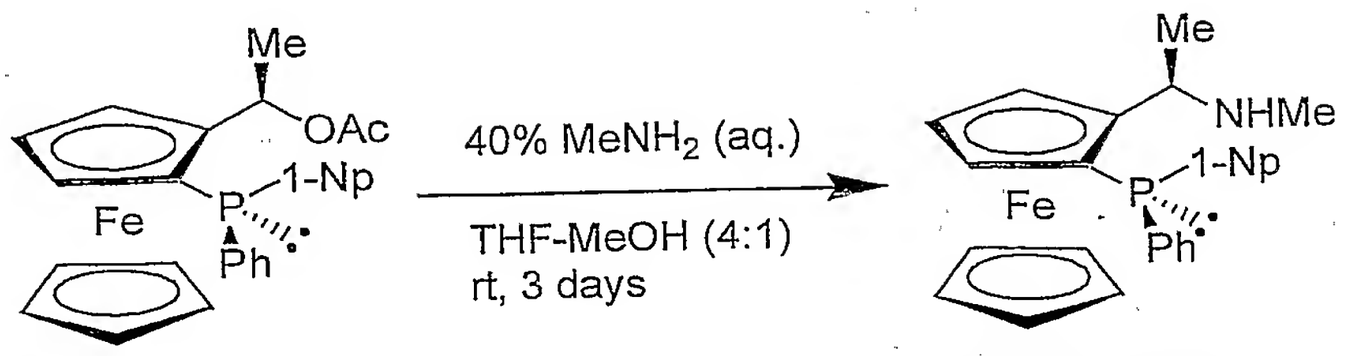


R_C-S_{Fe}-S_P-**6** R_C-S_{Fe}-S_P-**9**

A solution of (R_c, S_{Fe}, S_P)-**6** (633 mg, 1.25 mmol) and 40% methylamine aqueous solution (3.0 mL) in THF (10 mL) and MeOH (2.5 mL) was stirred for 3 days at room temperature, and concentrated. The residue was dissolved in Et_2O (20 mL), washed with brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by chromatography (SiO_2, hexane-EtOAc-Et3N = 85:10:5) to give the title compound (549 mg, 92%) as orange crystals. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.49 (d, 3H, *J* = 6.6 Hz); 2.07 (s, 3H); 3.69 (s, 5H); 3.95 (m, 1H); 4.01 (m, 1H); 4.31 (t, 1H, *J* = 2.5 Hz); 4.48 (m, 1H); 7.23 (m, 5H); 7.39 ~ 7.47 (m, 2H); 7.54 (m, 1H); 7.66 (m, 1H); 7.90 (t, 2H, *J* = 7.9 Hz), 9.25 (dd, 1H, *J* = 7.9 and 6.7 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz): δ –39.91.

Example 10

(R_c, S_{Fe}, R_P)-2-[(1- N-Methylamino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_c, S_{Fe}, R_P)-10]:

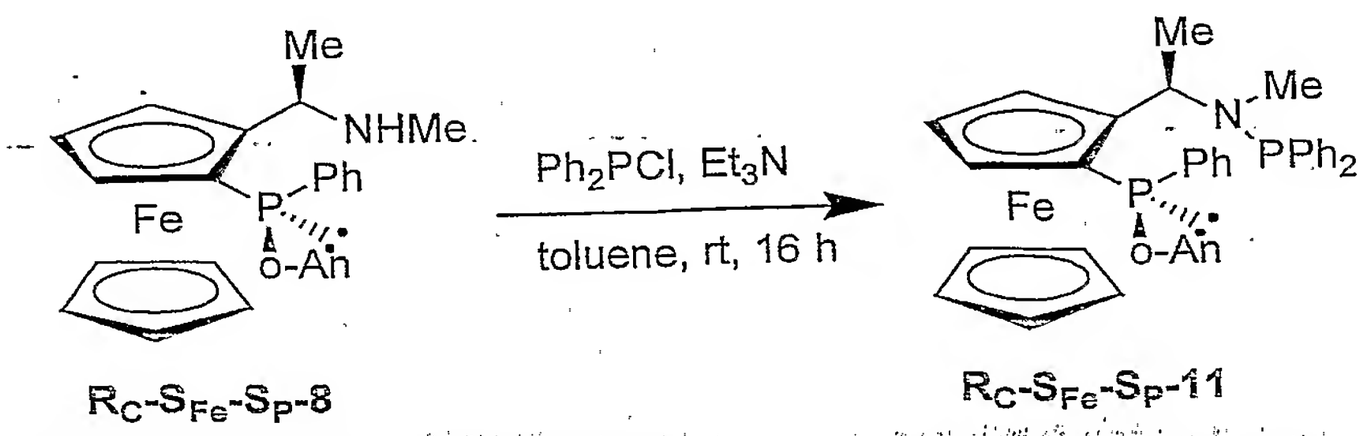


R_C-S_{Fe}-R_P-7 **R_C-S_{Fe}-R_P-10**

A solution of (R_c, S_{Fe}, R_P)-**7** (633 mg, 1.25 mmol) and 40% methylamine aqueous solution (3.0 mL) in THF (10 mL) and MeOH (2.5 mL) was stirred for 3 days at room temperature, and concentrated. The residue was dissolved in Et_2O (20 mL), washed with brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by chromatography (SiO_2, hexane-EtOAc-Et3N = 85:10:5) to give the title compound (537 mg, 90%) as orange crystals. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.45 (d, 3H, J = 6.5 Hz); 1.83 (s, 3H); 3.82 (m, 1H); 3.97 (m, 1H); 4.07 (s, 5H); 3 4.35 (t, 1H, J = 2.5 Hz); 4.53 (m, 1H); 7.20 (m, 1H); 7.30 ~ 7.36 (m, 5H); 7.40 (m, 1H); 7.56 ~ 7.61 (m, 2H); 7.78 (t, 2H, J = 8.2 Hz), 8.38 (m, 1H). ^{31}P NMR ($CDCl_3$, 162 MHz): δ – 32.25.

Example 11

(R_C, S_{Fe}, S_P)-2-[1-[(N-Methyl-N-diphenylphosphino)amino]ethyl]-1-[(2-methoxyphenyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-11]:

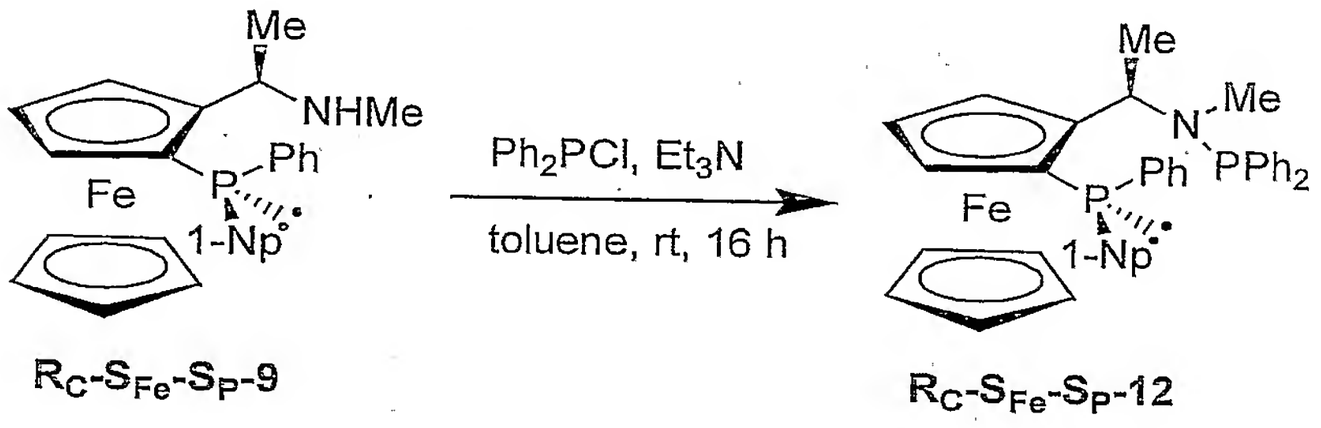


R_C-S_{Fe}-S_P-8 **R_C-S_{Fe}-S_P-11**

To a solution of (R_c, S_{Fe}, S_P)-**8** (457 mg, 1.0 mmol) and Et3N (0.28 mL, 2.0 mmol) in toluene (2.5 mL) was added dropwise chlorodiphenylphosphine (188 uL, 1.05 mmol) at 0 °C. Then the mixture was warmed to room temperature, and stirred overnight (16 h) at room temperature, and filtered through a pad of neutral aluminium oxide and eluted with hexane-EtOAc (9:1) to afford the title compound (570 mg, 89%) as orange foam. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.55 (d, 3H, *J* = 6.9 Hz); 2.17 (d, 3H, *J* = 3.4 Hz); 3.87 (s, 8H, overlap); 4.24 (m, 1H); 4.38 (t, 1H, *J* = 2.4 Hz); 4.53 (m, 1H); 4.88 (m, 1H); 6.88 ~ 6.96 (m, 6H); 7.03 ~ 7.14 (m, 6H); 7.20 ~ 7.37 (m, 7H). ^{31}P NMR ($CDCl_3$, 162 MHz): δ 56.93, –38.64.

Example 12

(R_c, S_{Fe}, S_P)-2-[1-[(N-Methyl-N-diphenylphosphino)amino]ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_c, S_{Fe}, S_P)-12]:



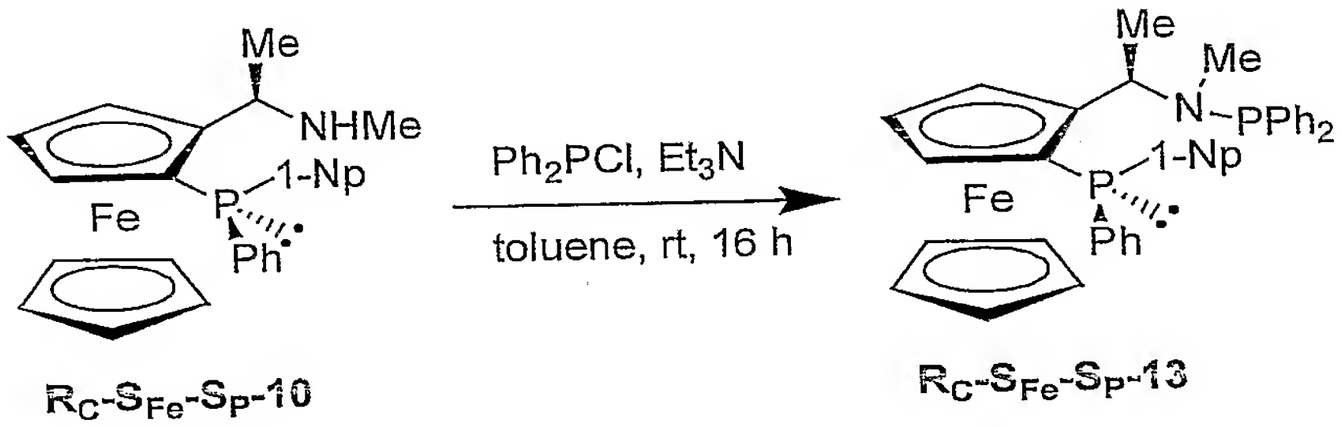
R_C-S_{Fe}-S_P-9 R_C-S_{Fe}-S_P-12

To a solution of (R_c, S_{Fe}, S_P)-**9** (477 mg, 1.0 mmol) and Et_3N (0.28 mL, 2.0 mmol) in toluene (2.5 mL) was added dropwise chlorodiphenylphosphine (188 uL, 1.05 mmol) at 0 °C. Then the mixture was warmed to room temperature,

and stirred overnight (16 h) at room temperature, and filtered through a pad of neutral aluminium oxide and eluted with hexane-EtOAc (9:1) to afford the title compound (595 mg, 90%) as orange foam.. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.53 (d, 3H, *J* = 6.8 Hz); 2.22 (d, 3H, *J* = 3.3 Hz); 3.44 (s, 5H); 4.26 (m, 1H); 4.39 (t, 1H, *J* = 2.4 Hz); 4.50 (m, 1H); 5.03 (m, 1H); 6.85 ~ 6.94 (m, 4H); 7.04 (tt, 1H, *J* = 7.2 and 1.4 Hz); 7.09 ~ 7.19 (m, 4H); 7.27 ~ 7.31 (m, 4H); 7.37 ~ 7.43 (m, 3H); 7.48 ~ 7.56 (m, 2H); 7.68 (m, 1H); 7.89 (dd, 2H, *J* = 8.1 and 4.8 Hz); 9.44 (t, 1H, *J* = 7.6 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz): δ 59.59, –41.03.

Example 13

(R_C, S_{Fe}, R_P)-2-[1-[(N-Methyl-N-diphenylphosphino)amino]ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, R_P)-13]:



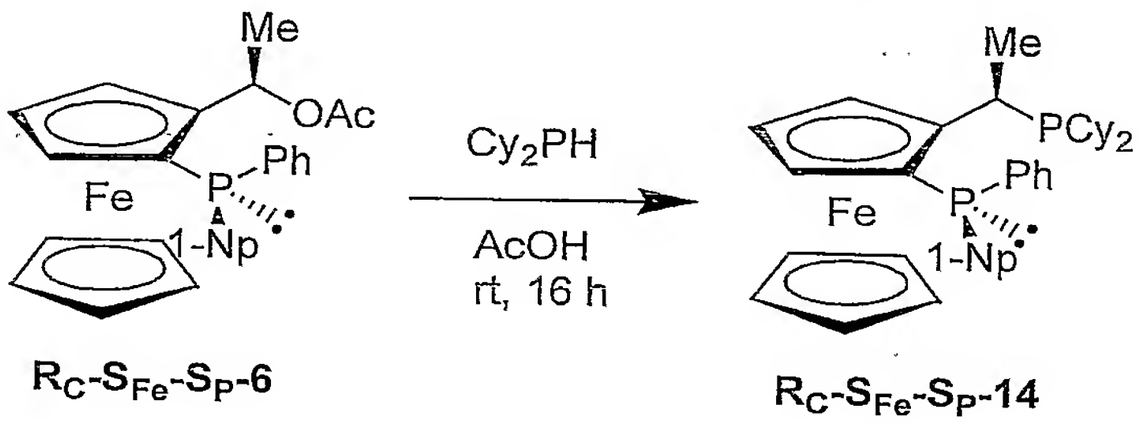
R_C-S_{Fe}-S_P-10 R_C-S_{Fe}-S_P-13

To a solution of (R_C, S_{Fe}, R_P)-**10** (239 mg, 1.0 mmol) and Et_3N (0.14 mL, 1.0 mmol) in toluene (2.0 mL) was added dropwise chlorodiphenylphosphine (89 uL, 0.50 mmol) at 0 °C. Then the mixture was warmed to room temperature, and stirred overnight (16 h) at room temperature, and filtered through a pad of neutral aluminium oxide and eluted with hexane-EtOAc (9:1) to afford the title compound (304 mg, 992%) as orange foam. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ

1.51 (d, 3H, J = 6.8 Hz); 2.08 (d, 3H, J = 3.5 Hz); 3.90 (s, 5H); 4.15 (m, 1H); 4.44 (t, 1H, J = 2.4 Hz); 4.58 (m, 1H); 5.02 (m, 1H); 6.44 (td, 2H, J = 8.0 and 1.8 Hz); 6.62 (td, 2H, J = 8.0 and 1.2 Hz); 6.80 (tt, 1H, J = 7.4 and 1.2 Hz); 7.20 (m, 1H); 7.15 ~ 7.30 (m, H); 7.58 ~ 7.64 (m, H); 7.70 (dd, 1H, J = 6.8 and 1.8 Hz); 7.79 (d, 1H, J = 8.0 Hz); 8.20 (dd, 1H, J = 8.2 and 2.4 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz): δ 58.81, –31.16.

Example 14

(R_C, S_{Fe}, S_P)-2-(1-Dicyclohexylphosphino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-14]:



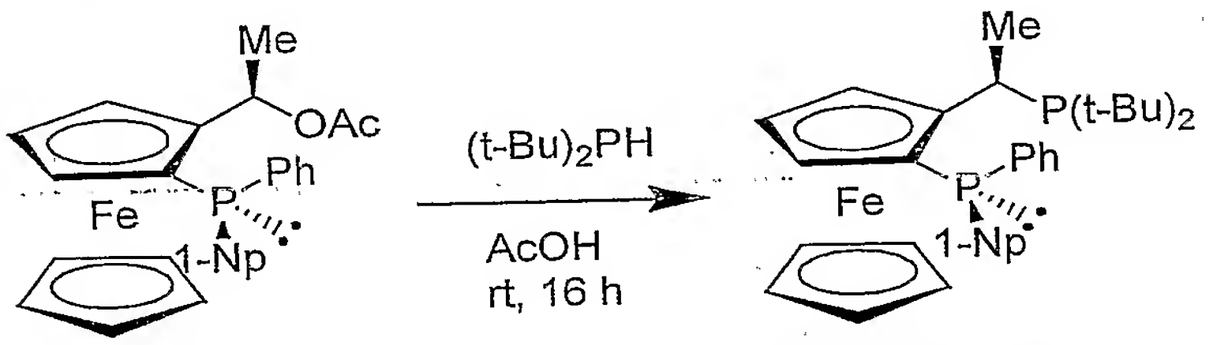
R_C-S_{Fe}-S_P-6 **R_C-S_{Fe}-S_P-14**

A solution of (R_C, S_{Fe}, S_P)-**6** (506 mg, 1.0 mmol) and dicyclohexylphosphine (243 uL, 1.2 mmol) in acetic acid (3 mL) was stirred overnight at room temperature, and poured into 10% K_2CO_3 aqueous solution (60 mL) with stirring, extracted with Et_2O (2×25 mL). The combined ether layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc = 9:1) to afford the title compound (614 mg, 95%) as orange crystals. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.14 (br. m, 10H); 1.57 (br. m, 10H); 3.22 (m, 1H); 3.40 (s, 5H); 4.08 (m, 1H); 4.23 (t, 1H, J = 2.4 Hz); 4.31 (m, 1H);

7.16 ~ 7.22 (m, 5H); 7.36 (dd, 1H, J = 8.0 and 7.2 Hz); 7.45 ~ 7.49 (m, 2H); 7.60 (ddd, 1H, J = 8.5, 6.8 and 1.4 Hz); 7.82 (t, 2H, J = 8.1 Hz); 9.28 (dd, 1H, J = 7.6 and 6.8 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz): δ 17.46 (d, J = 27.7 Hz); –42.43 (d, J = 27.7 Hz).

Example 15

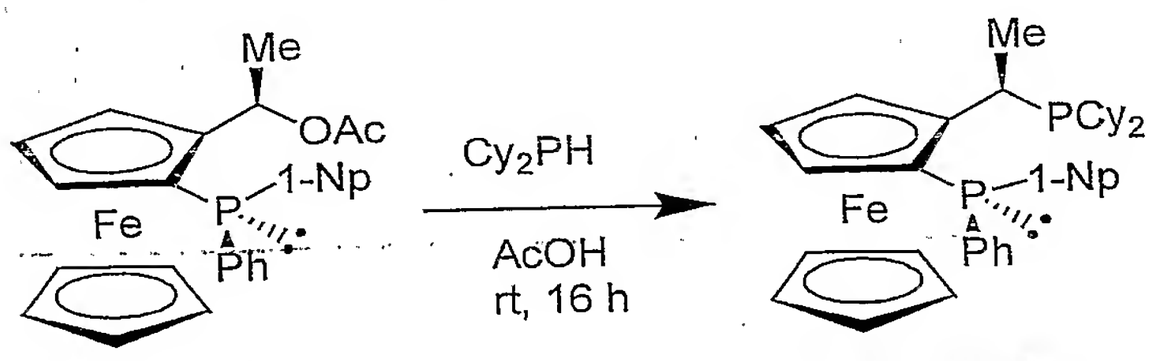
(R_C, S_{Fe}, S_P)-2-(1-Di-tert-butylphosphino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-15]:



R_C-S_{Fe}-S_P-6 **R_C-S_{Fe}-S_P-15**

Example 16

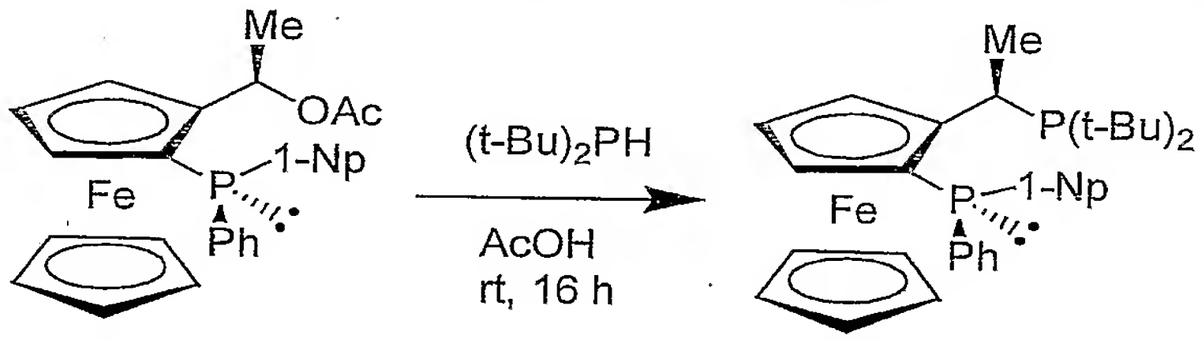
(R_C, S_{Fe}, R_P)-2-(1-Dicyclohexylphosphino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, R_P)-16]:



R_C-S_{Fe}-R_P-7 **R_C-S_{Fe}-R_P-16**

Example 17

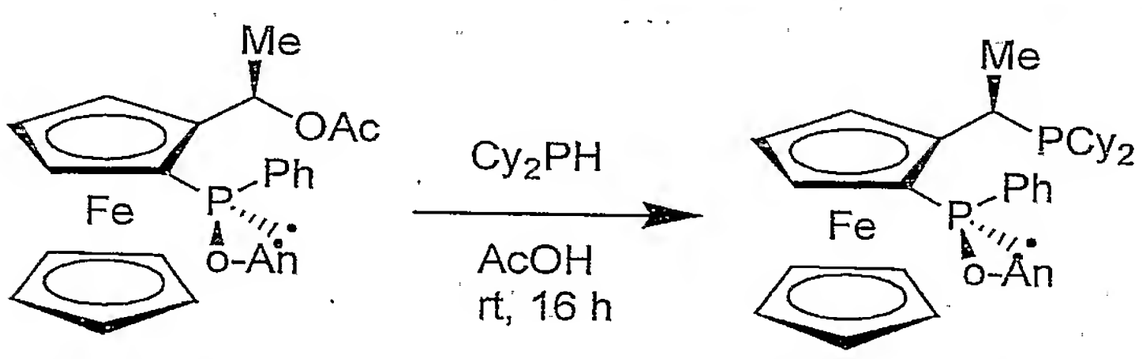
(R_C, S_{Fe}, R_P)-2-(1-Di-tert-butylphosphino)ethyl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, R_P)-17]:



R_C-S_{Fe}-R_P-7 R_C-S_{Fe}-R_P-17

Example 18

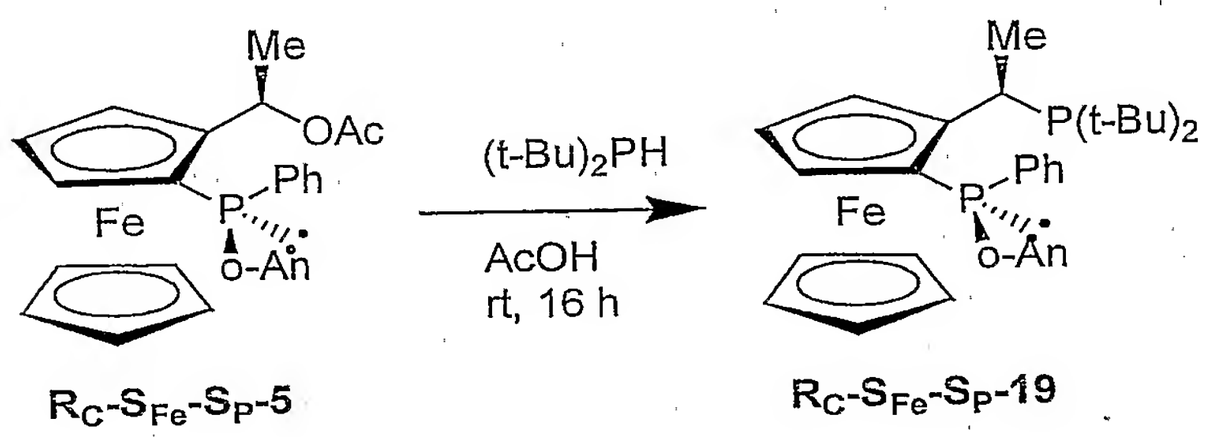
(R_C, S_{Fe}, S_P)-2-(1-Dicyclohexylphosphino)ethyl]-1-[(2-methoxyphenyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-18]:



R_C-S_{Fe}-S_P-5 R_C-S_{Fe}-S_P-18

Example 19

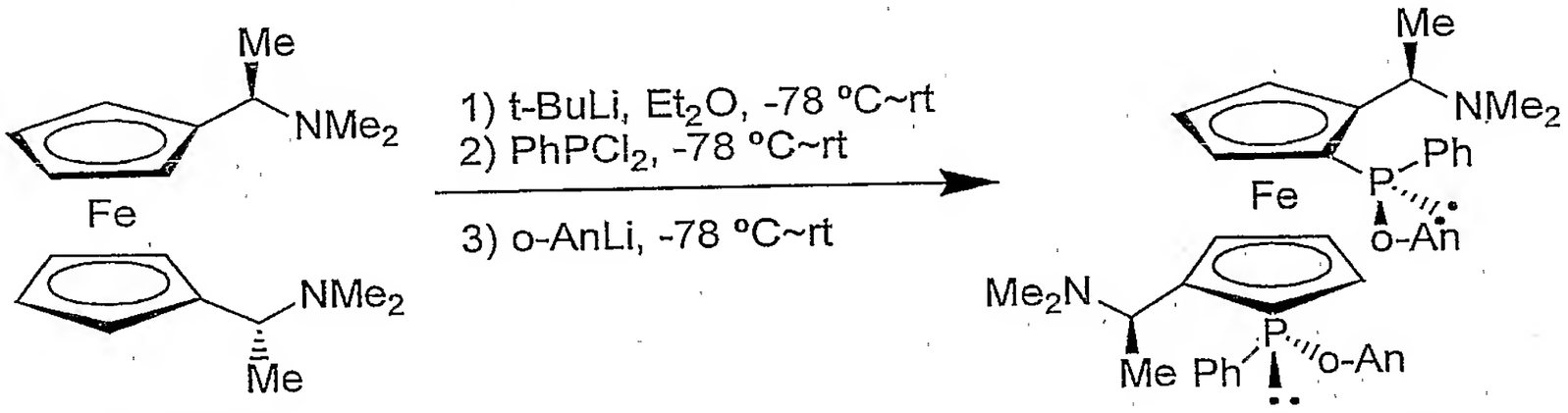
(R_C, S_{Fe}, S_P)-2-(1-Di-tert-butylphosphino)ethyl]-1-[(2-methoxyphenyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-19]:



R_C-S_{Fe}-S_P-5 R_C-S_{Fe}-S_P-19

Example 20

(R_C, S_{Fe}, S_P)-2,2'-Bis[(1-N,N-dimethylamino)ethyl]-1,1'-bis[(2-methoxyphenyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-21]:



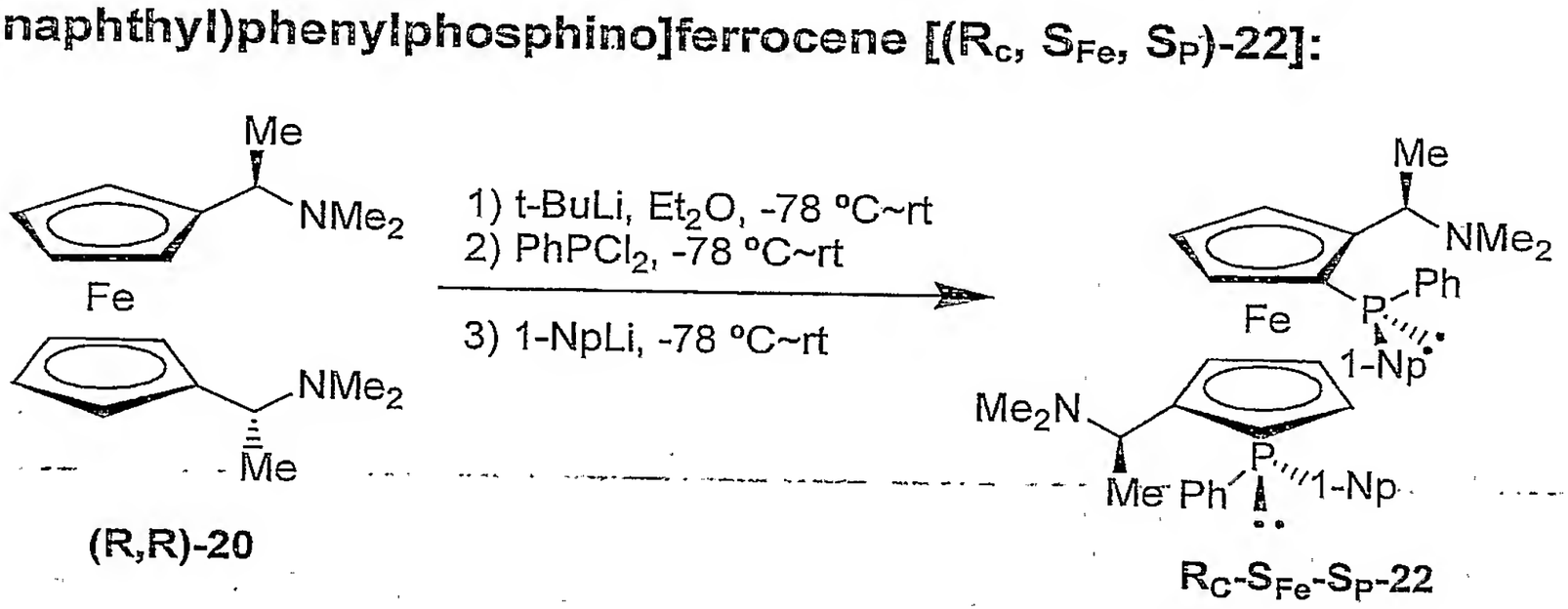
(R,R)-20 R_C-S_{Fe}-S_P-21

To a solution of (R,R)-1,1'-bis(1-N,N-dimethylaminoethyl)ferrocene [(R,R)-20] (986 mg, 3.0 mmol) in Et_2O (30 mL) was added 1.5 M t-BuLi solution in pentane (6.0 mL, 9 mmol) over 10 min via a syringe at –78 °C. After addition was completed, the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The resulting red solution was cooled to –78 °C again, and dichlorophenylphosphine (1.22 mL, 9.0 mmol) was added in one portion.

After stirring for 10 min at –78 °C, the mixture was slowly warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then cooled to –78 °C again, and a solution of (2-methoxy)phenyllithium [prepared from 2-bromoanisole (1.87 g, 10 mmol) and 1.5 M t-BuLi solution in pentane (13.3 mL, 20 mmol) in Et_2O (50 mL) at –78 °C] was added slowly via a cannula. The mixture was warmed to room temperature overnight, and filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc-Et_3N = 80:15:5) to afford the title compound (1.10 g, 48%) as yellow foam. ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.28 (d, 6H, J = 6.7 Hz); 1.71 (s, 12H); 3.16 (m, 2H); 3.84 (s, 6H); 4.05 (m, 2H); 4.16 (m, 2H); 4.53 (t, 2H, J = 2.3 Hz); 6.62 (t, 2H, J = 7.4 Hz); 6.73 (dd, 2H, J = 8.1 and 4.6 Hz); 6.85 (ddd, 2H, J = 7.4, 5.3 and 1.8 Hz); 7.03 ~ 7.11 (m, 10H); 7.17 (td, 2H, J = 8.5 and 1.6 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ –39.53 (s).

Example 21

(R_C, S_{Fe}, S_P)-2,2'-Bis[(1-N,N-dimethylamino)ethyl]-1,1'-bis[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-22]:



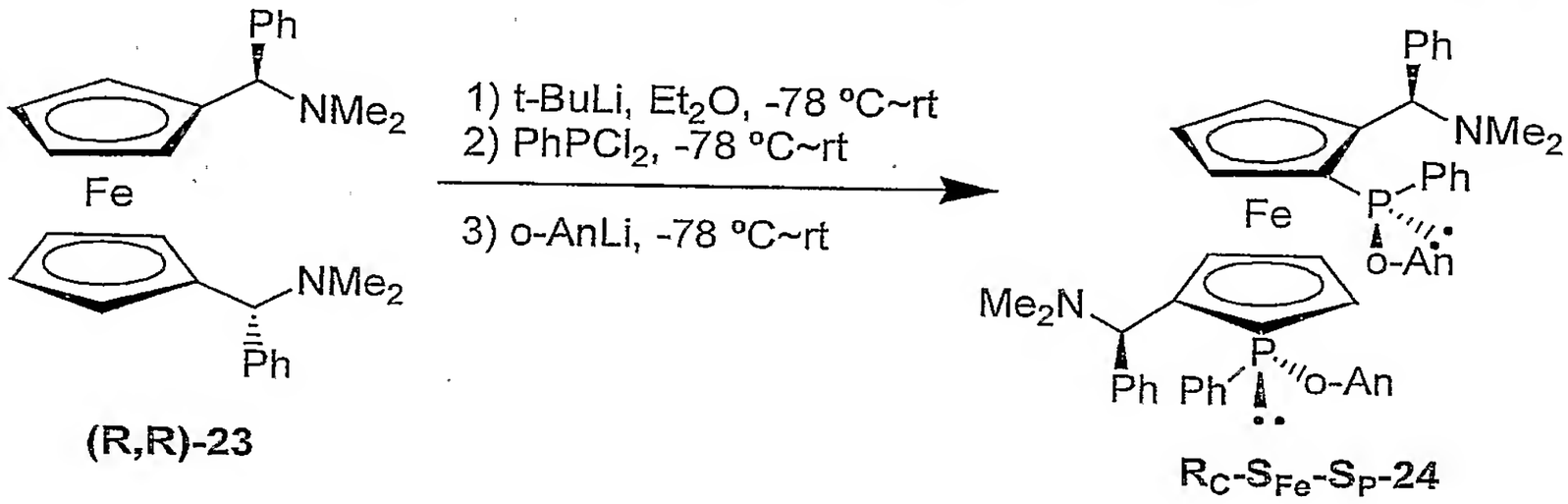
(R,R)-20

R_C-S_{Fe}-S_P-22

To a solution of (R,R)-1,1'-bis(1-N,N-dimethylaminoethyl)ferrocene [(R,R)-20] (986 mg, 3.0 mmol) in Et_2O (30 mL) was added 1.5 M t-BuLi solution in pentane (6.0 mL, 9 mmol) over 10 min via a syringe at –78 °C. After addition was completed, the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The resulting red solution was cooled to –78 °C again, and dichlorophenylphosphine (1.22 mL, 9.0 mmol) was added in one portion. After stirring for 10 min at –78 °C, the mixture was slowly warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then cooled to –78 °C again, and a solution of 1-naphthyllithium [prepared from 1-bromonaphthalene (2.07 g, 10 mmol) and 1.5 M t-BuLi solution in pentane (13.3 mL, 20 mmol) in Et_2O (50 mL) at –78 °C] was added slowly via a cannula. The mixture was warmed to room temperature overnight, and filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc-Et_3N = 80:15:5) to afford the title compound (827 mg, 35%) as yellow crystals. ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.28 (d, 6H, J = 6.8 Hz); 1.74 (s, 12H); 2.49 (m, 2H); 4.01 (t, 2H, J = 2.3 Hz); 4.06 (m, 2H); 4.08 (m, 2H); 6.87 ~ 6.93 (m, 4H); 6.99 ~ 7.09 (m, 10H); 7.50 (td, 2H, J = 8.1 and 1.1 Hz); 7.53 (td, 2H, J = 6.8 and 1.3 Hz); 7.70 (d, 2H, J = 8.1 Hz); 7.83 (d, 2H, J = 8.1 Hz); 9.16 (t, 2H, J = 7.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ –39.47 (s).

Example 22

(R_C, S_{Fe}, S_P)-2,2'-Bis[(α-N,N-dimethylamino)phenylmethyl]-1,1'-bis[(2-methoxyphenyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-24]:

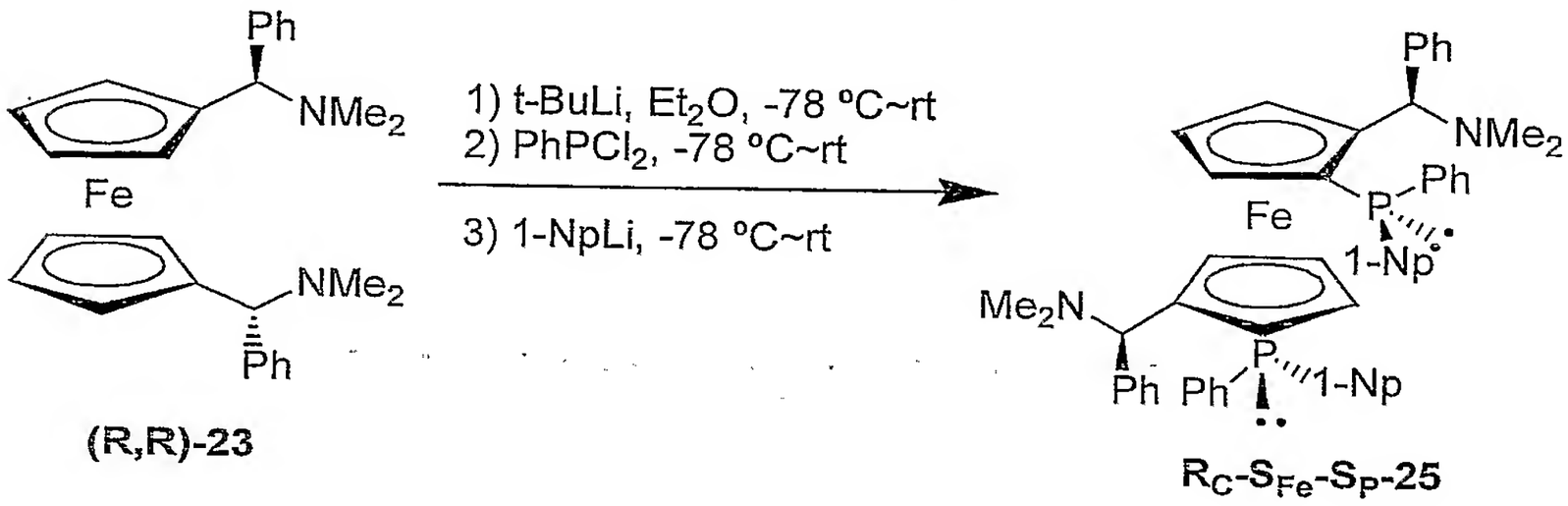


(R,R)-23

R_C-S_{Fe}-S_P-24

Example 23

(R_C, S_{Fe}, S_P)-2,2'-Bis[(α-N,N-dimethylamino)phenylmethyl]-1,1'-bis[(1-naphthyl)phenylphosphino]ferrocene [(R_C, S_{Fe}, S_P)-25]:



(R,R)-23

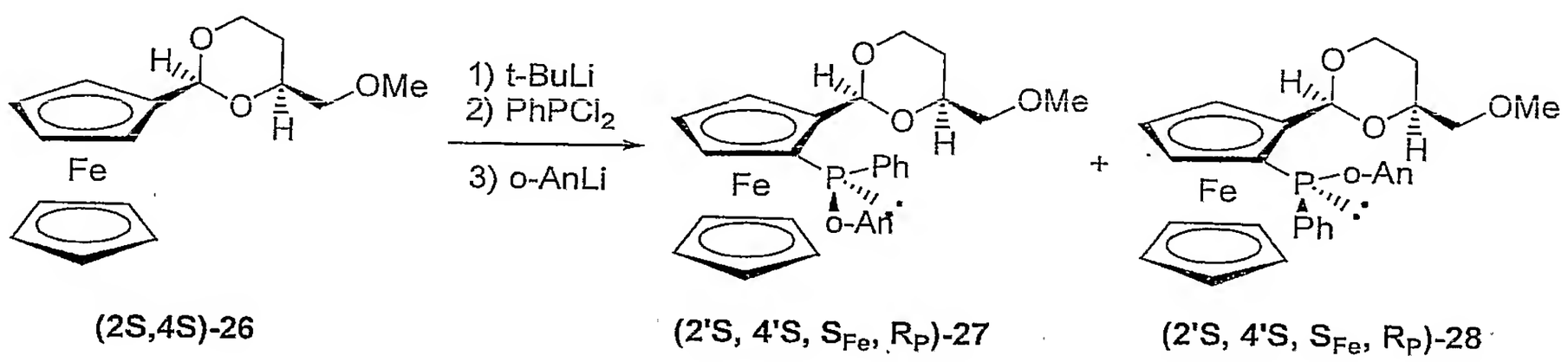
R_C-S_{Fe}-S_P-25

To a solution of (R,R)-1,1'-bis[(α-N,N-dimethylamino)phenylmethyl]ferrocene [(R,R)-23] (903 mg, 2.0 mmol) in Et_2O (20 mL) was added 1.5 M t-BuLi solution in pentane (4.0 mL, 6 mmol) over 10 min via a syringe at –78 °C. After addition was completed, the mixture was warmed to room temperature, and stirred for

1.5 h at room temperature. The resulting red solution was cooled to –78 °C again, and dichlorophenylphosphine (814 uL, 6.0 mmol) was added in one portion. After stirring for 10 min at –78 °C, the mixture was slowly warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then cooled to –78 °C again, and a solution of 1-naphthyllithium [prepared from 1-bromonaphthalene (1.45 g, 7 mmol) and 1.5 M t-BuLi solution in pentane (9.3 mL, 14 mmol) in Et_2O (40 mL) at –78 °C] was added slowly via a cannula. The mixture was warmed to room temperature overnight, and filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc = 3:1) to afford the title compound (369 mg, 20%) as orange crystals. ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.54 (s, 12H); 2.43 (m, 2H); 2.98 (br. s, 2H); 3.96 (t, 2H, *J* = 2.3 Hz); 4.42 (d, 2H, *J* = 5.3 Hz); 6.67 (dd, 2H); 6.96 ~ 7.34 (m, 22H); 7.55 (, 2H, *J* = Hz); 7.67 (, 4H, *J* = Hz); 7.84 (, 2H, *J* = Hz); 9.21 (t, 2H, *J* = 7.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ – (s).

Example 24

(2'S, 4'S, S_{Fe}, S_P)-[4'-(methoxymethyl-1,3-dioxan-2'-yl]-1-[(2-methoxyphenyl)phenylphosphino]ferrocene [(2'S, 4'S, S_{Fe}, S_P)-27] and (2'S, 4'S, S_{Fe}, R_P)-[4'-(methoxymethyl-1,3-dioxan-2'-yl]-1 [(2-methoxyphenyl)phenylphosphino]ferrocene [(2'S, 4'S, S_{Fe}, R_P)-28]:



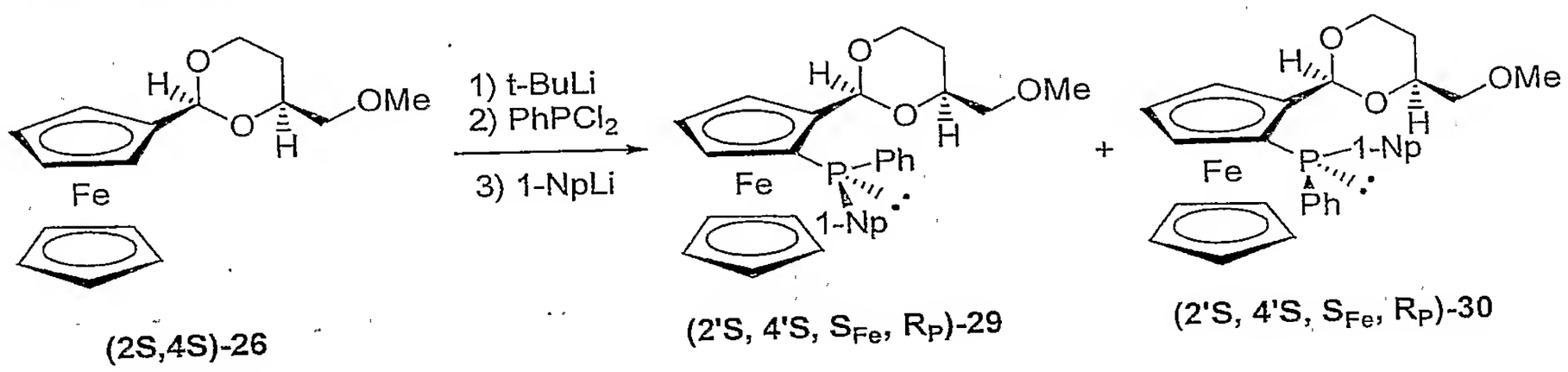
(2S,4S)-26 **(2'S, 4'S, S_{Fe}, R_P)-27** **(2'S, 4'S, S_{Fe}, R_P)-28**

To a solution of (2S,4S)-4-(methoxymethyl)-2-ferrocenyl-1,3-dioxane [(2S,4S)-26] (1.58 g, 5 mmol) in Et_2O (20 mL) was added 1.7 M t-BuLi solution in pentane (3.23 mL, 5.5 mmol) at –40 °C. After stirring for 10 min, the cooling bath was removed and the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The resulting orange suspension was cooled to –78 °C, and dichlorophenylphosphine (750 uL, 5.5 mmol) was added in one portion. After stirring for 10 min, the cooling bath was removed and the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was cooled to –78 °C again, a solution of 2-methoxyphenyllithium [prepared from 2-bromoanisole (1.22 mL, 6.5 mmol) and 1.7 M t-BuLi solution in pentane (7.6 mL, 13 mmol) in Et_2O (40 mL) at –78 °C] was added slowly via a cannula. The mixture was warmed to room temperature overnight, and filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc = 6:1) to afford the title compound (2.41 g, 91%) as a mixture of two diastereomers (in about 3.3:1 ratio). After repeated chromatography and recrystallisation from hexane, the two diastereomers were separated to give the major product [(2'S, 4'S, S_{Fe}, R_P)-**28** ?] and the minor product. Major product: ^1H NMR ($CDCl_3$,

400.13 MHz): δ 1.42 (dm, 1H, J = 13.3 Hz); 1.74 (m, 1H); 2.89 (d, 2H, J = 5.1 Hz); 3.03 (s, 3H); 3.59 (m, 1H); 3.60 (s, 3H); 3.74 (m, 1H); 3.91 (td, 1H, J = 12.2 and 2.5 Hz); 4.08 (s, 5H); 4.24 ~4.27 (m, 2H); 4.70 (m, 1H); 5.71 (d, 1H, J = 2.5 Hz); 6.74 (dd, 1H, J = 7.9 and 4.6 Hz); 6.80 ~ 6.86 (m, 2H); 7.22 (m, 1H); 7.31 ~ 7.35 (m, 3H); 7.51 ~7.56 (m, 2H). ^{31}P NMR ($CDCl_3$, 162 MHz): δ – 31.46 (s).

Example 25

(2'S, 4'S, S_{Fe}, S_P)-[4'-(methoxymethyl-1,3-dioxan-2'-yl]-1-[(1-naphthyl)phenylphosphino]ferrocene [(2'S, 4'S, S_{Fe}, S_P)-29] and (2'S, 4'S, S_{Fe}, R_P)-[4'-(methoxymethyl-1,3-dioxan-2'-yl]-1 [(1-naphthyl)phenylphosphino]ferrocene [(2'S, 4'S, S_{Fe}, R_P)-30]:



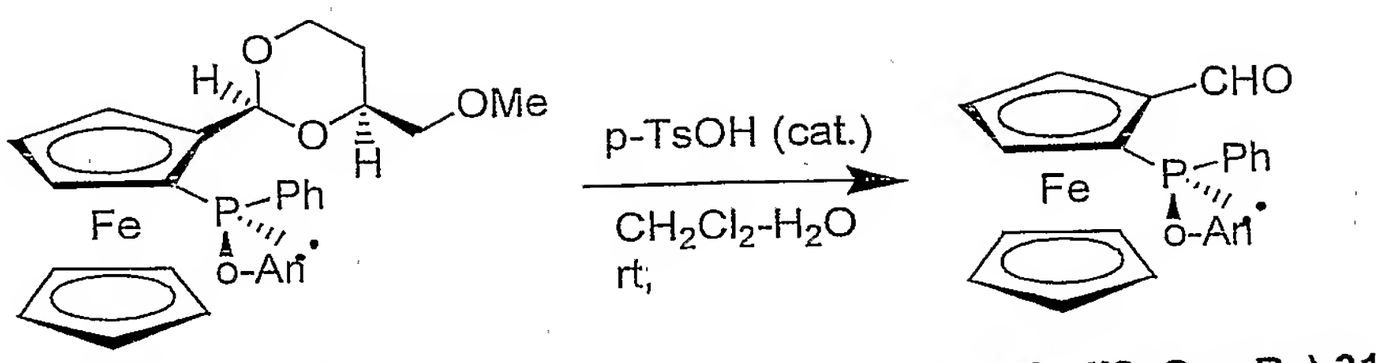
(2S,4S)-26 (2'S, 4'S, S_{Fe}, R_P)-29 (2'S, 4'S, S_{Fe}, R_P)-30

To a solution of (2S,4S)-4-(methoxymethyl)-2-ferrocenyl-1,3-dioxane [(2S,4S)-26] (3.16 g, 10 mmol) in Et_2O (40 mL) was added 1.5 M t-BuLi solution in pentane (7.4 mL, 11 mmol) at –40 °C. After stirring for 10 min, the cooling bath was removed and the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The resulting orange suspension was cooled to –78

°C, and dichlorophenylphosphine (1.49 mL, 11 mmol) was added in one portion. After stirring for 10 min, the cooling bath was removed and the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was cooled to –78 °C again, a solution of 1-naphthyllithium [prepared from 1-bromonaphthalene (1.67 mL, 12 mmol) and 1.5 M t-BuLi solution in pentane (16 mL, 24 mmol) in Et_2O (60 mL) at –78 °C] was added slowly via a cannula. The mixture was warmed to room temperature overnight, and filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc = 6:1) to afford the title compound (%) as a mixture of two diastereomers (in about 3.4:1 ratio), which was recrystallised from hexane to give the pure major product [(2'S, 4'S, S_{Fe}, R_P)-**30** ?] (%) as yellow needles. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.33 (dm, 1H, *J* = 13.3 Hz); 1.63 (m, 1H); 2.56 (dd, 1H, *J* = 10.3 and 4.8 Hz); 2.67 (dd, 1H, *J* = 10.3 and 5.6 Hz); 2.76 (s, 3H); 3.58 (m, 1H); 3.67 (m, 1H); 3.86 (td, 1H, *J* = 12.2 and 2.5 Hz); 4.15 (s, 5H); 3.74 (m, 1H); 4.21 (ddd, 1H, *J* = 11.4, 5.1 and 1.0 Hz); 4.31 (t, 1H, *J* = 2.5 Hz); 4.74 (m, 1H); 5.69 (d, 1H, *J* = 2.5 Hz); 7.16 (ddd, 1H, *J* = 7.1, 5.1 and 1.2 Hz); 7.29 ~ 7.40 (m, 6H); 7.54 ~ 7.58 (m, 2H); 7.74 (d, 1H, *J* = 8.3 Hz); 7.78 (d, 1H, *J* = 8.0 Hz); 8.25 ~8.28 (m, 1H). ^{31}P NMR ($CDCl_3$, 162 MHz): δ – 28.03 (s).

Example 26

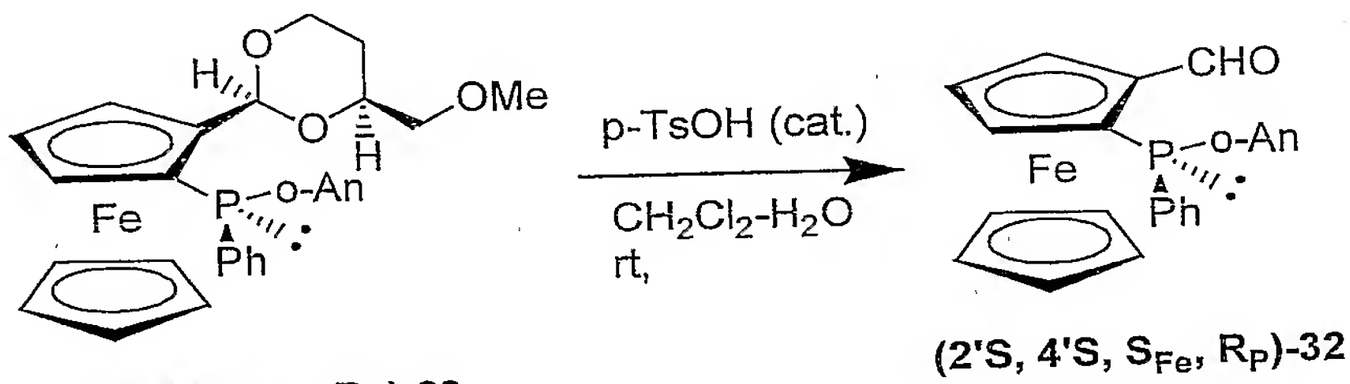
(S_{Fe}, S_P)-2-[(2-Methoxyphenyl)phenylphosphino]ferrocenecarboxaldehyde [(S_{Fe}, S_P)-31]:



(2'S, 4'S, S_{Fe}, R_P)-27 **(2'S, 4'S, S_{Fe}, R_P)-31**

Example 27

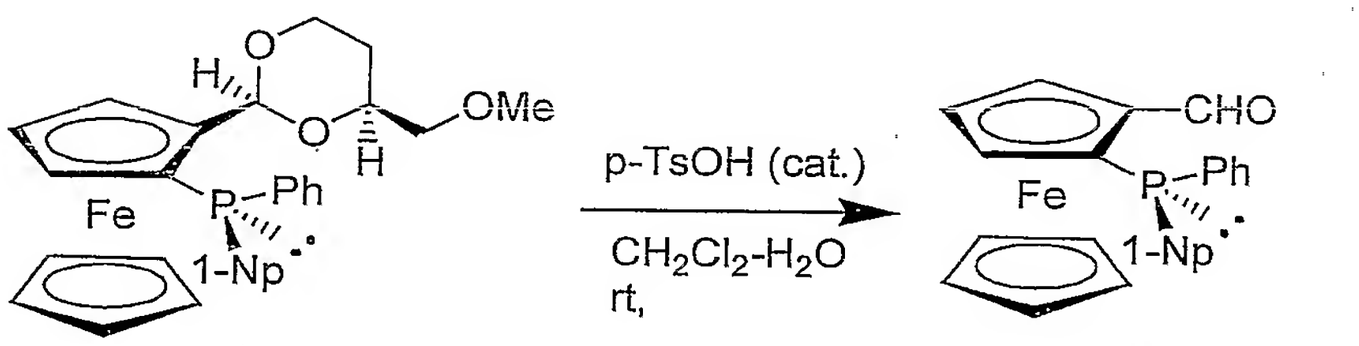
(S_{Fe}, R_P)-2-[(2-Methoxyphenyl)phenylphosphino]ferrocenecarboxaldehyde [(S_{Fe}, R_P)-32]:



(2'S, 4'S, S_{Fe}, R_P)-28 **(2'S, 4'S, S_{Fe}, R_P)-32**

Example 28

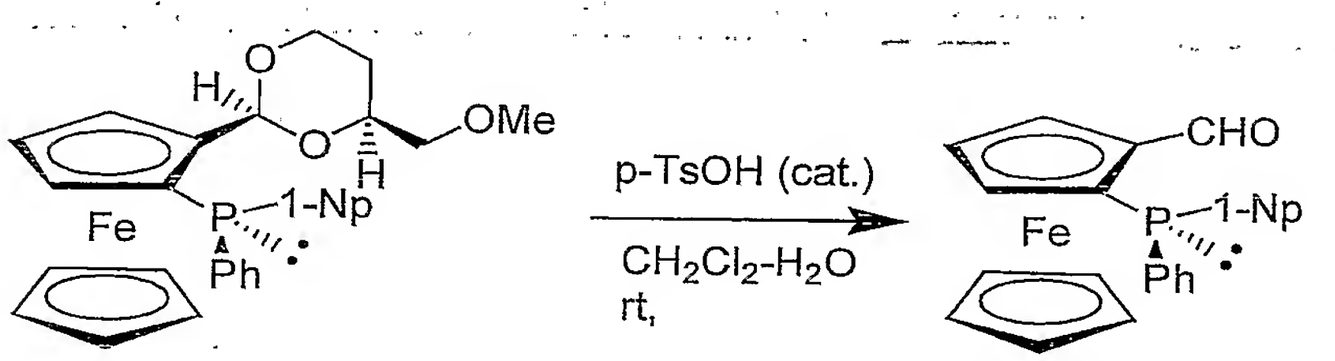
(S_{Fe}, S_P)-2-[(1-Naphthyl)phenylphosphino]ferrocenecarboxaldehyde [(S_{Fe}, S_P)-33]:



(2'S, 4'S, S_{Fe}, R_P)-29 **(2'S, 4'S, S_{Fe}, R_P)-33**

Example 29

(S_{Fe}, R_P)-2-[(1-Naphthyl)phenylphosphino]ferrocenecarboxaldehyde [(S_{Fe}, R_P)-34]:



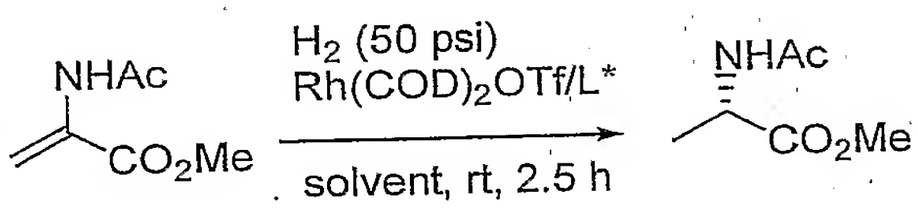
(2'S, 4'S, S_{Fe}, R_P)-30 **(2'S, 4'S, S_{Fe}, R_P)-34**

Asymmetric Hydrogenation-General Procedure:

Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate [$Rh(COD)_2TfO$] (2.3 mg, 5 umol) and the desired ligand (6 umol)) were placed in a vessel which was purged with argon. The desired solvent was degassed with Ar for 15 minutes, then 5.0 mL was added to the reaction vessel via syringe. This solution was stirred at 25 °C. under argon for 15 minutes. The desired substrate (1.0 mmol) was then added to the catalyst solution. The solution was then purged five times

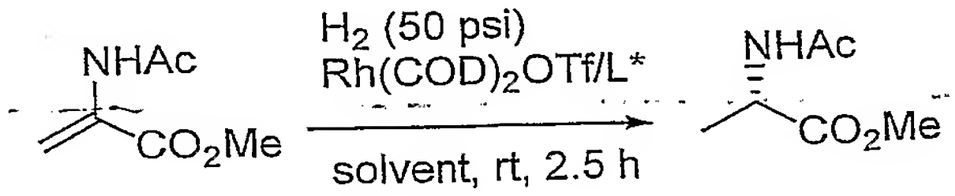
with argon and pressurized with hydrogen to the desired pressure and stirred at room temperature. The reactions were run for the desired time at the desired pressure, and then depressurized. Samples were taken and analyzed for enantiomeric excess using standard analytical techniques.

Example 30 N-Acetyl L-alanine methyl ester via Hydrogenation in THF:



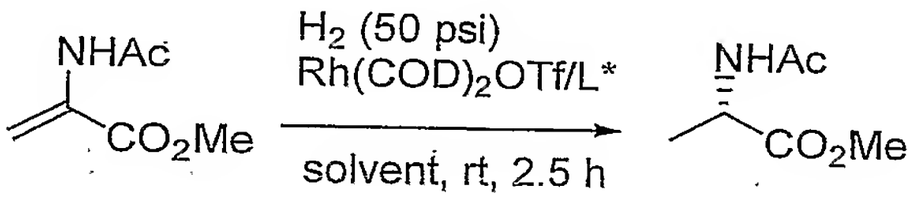
Methy 2-acetamidoacrylate (143 mg, 1.0 mmol) was hydrogenated according to General Procedure under 50psi of hydrogen in THF using bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 umol; 0.01 equiv) and ligand (R_c, S_{Fe}, S_P)-**11** (3.8 mg; 6 umol; 0.012 equiv) for 2.5 hour to afford 18.6% conversion to amino acid derivative with 88.6% ee as determined by chiral GC analysis.

Example 31 N-Acetyl L-alanine methyl ester via Hydrogenation in THF:



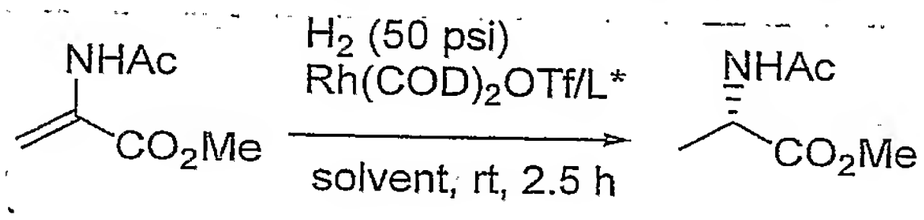
Methy 2-acetamidoacrylate (143 mg, 1.0 mmol) was hydrogenated according to General Procedure under 50psi of hydrogen in THF using bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 umol; 0.01 equiv) and ligand (R_c, S_{Fe}, S_P)-**12** (4.0 mg; 6 umol; 0.012 equiv) for 2.5 hour to afford 100% conversion to amino acid derivative with 98.3% ee as determined by chiral GC analysis.

Example 32 N-Acetyl L-alanine methyl ester via Hydrogenation in THF:



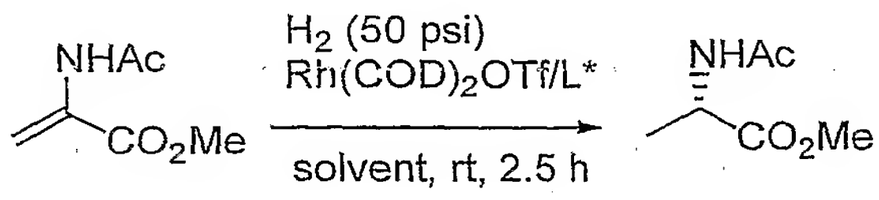
Methy 2-acetamidoacrylate (143 mg, 1.0 mmol) was hydrogenated according to General Procedure under 50psi of hydrogen in THF using bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 umol; 0.01 equiv) and ligand (R_c, S_{Fe}, S_P)-**13** (4.0 mg; 6 umol; 0.012 equiv) for 2.5 hour to afford 100% conversion to amino acid derivative with 92.3% ee as determined by chiral GC analysis.

Example 33 N-Acetyl L-alanine methyl ester via Hydrogenation in MeOH:



Methy 2-acetamidoacrylate (143 mg, 1.0 mmol) was hydrogenated according to General Procedure under 50psi of hydrogen in MeOH using bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 umol; 0.01 equiv) and ligand (R_c, S_{Fe}, S_P)-**12** (4.0 mg; 6 mumol; 0.012 equiv) for 2.5 hour to afford 100% conversion to amino acid derivative with >99% ee as determined by chiral GC analysis.

Example 34 N-Acetyl L-alanine methyl ester via Hydrogenation in THF wit (R_C, S_{Fe})-BoaPhoz:



Methy 2-acetamidoacrylate (143 mg, 1.0 mmol) was hydrogenated according to General Procedure under 50psi of hydrogen in THF using bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 umol; 0.01 equiv) and ligand (R_c, S_{Fe})-BoaPhoz (3.7 mg; 6 umol; 0.012 equiv) for 2.5 hour to afford 99% conversion to amino acid derivative with 94.5% ee as determined by chiral GC analysis.

References

1. T. Hayashi, in Ferrocenes, (Eds.: A. Togni, T. Hayashi), VCH, Weinheim, 1995, p. 105.
2. 2. Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.
3. 3. a. H. U. Blaser,W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Topics in Catalysis* **2002**, *19*, 3; b. H. U. Blaser, F.Spindler, M. Studer, *Applied Catal. A: General* **2001**, 221, 119.
4. 4. McGarrity, J.; Spindler, F.; Fuchs, R.; Eyer, M. (LONZA AG), EP-A 624587 A2, **1995**; *Chem. Abstr.* **1995**, *122*, P81369q.
5. 5. a. Blaser, H.-U. *Adv. Synth. Catal.* **2002**, *344*, 17. b. Blaser, H.-U.; Buser, H.-P.; Coers, K.; Hanreich, R.; Jalett, H.-P.; Jelsch, E.; Pugin, B.; Schneider, H.-D.; Spindler, F.; Wegmann, A. *Chimia* **1999**, *53*, 275.
6. 6. a. N. W. Boaz, S. D. Debenham, E. B. Mackenzie, S. E. Large, *Org. Lett.* **2002**, *4*, 2421. b. Boaz, N. W.; Debenham, S. D. *US 2002/0065417* (**2002**)
7. a) T. Ireland, G. Grossheimann, C. Wieser-Jeunesse, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 3212. b) T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem. Eur. J.* **2002**, *8*, 843;
8. a) M. Lotz, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 4708. b) K. Tappe; P. Knochel, *Tetrahedron: Asymmetry* **2004**, *15*, 12; c) M. Lotz, P. Knochel, A. Monsees, T. Riermeier, R. Kadyrov, J. J. Almena Perea, Ger. Pat. No. DE 10219490 (Degussa AG).

9. a) T. Sturm, L. Xiao, W. Weissensteiner, Chimia 2001,55, 688; b) W. Weissensteiner, T. Sturm, F. Spindler, *Adv. Synth. Catal.* **2003**, *345*, 160; c) Weissensteiner, T. Sturm, F. Spindler, US2003212284.

10. a. Perea, A. J. J.; Borner, A.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 8073. b. Perea, A. J. J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 375. c.Lotz, M.; Ireland, T.; Perea, A. J. J.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1839. d. Knochel, P.; Perea, A. J. J.; Drauz, K.; Klement, I. *US 6,284,925* (2001).

11. (a) Sawamura, M.; Hamashima, H.; Sugawara, M.; Kuwano, N.; Ito, Y. *Organometallics* **1995**, *14*, 4549. (b) Sawamura, M.;Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602. (c) Kuwano, R.; Sawamura, M.; Ito, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2521. (d) Kuwano, R.; Okuda, S.; Ito, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2773. (e) Kuwano, R.; Okuda, S.; Ito, Y. *J. Org. Chem.* **1998**, 63, 3499. (f) Kuwano, R.; Ito, Y. *J. Org. Chem.* **1999**, *64*, 1232. (g) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614.

12. a) Kang, J.; Lee, J. H.; Ahn, S. H.; Choi, J. S. *Tetrahedron Lett.* **1998**, *39*, 5523. b) Kang, J.; Lee, J. H.; Kim, J. B.; Kim, G. J. *Chirality* **2000**, *12*, 378.

13. a) Jendralla, H. ; Paulus, E. *Synlett*, **1997**, 471. b) Jendralla, J. H. *US 5,856,540* (**1999**)

14. a) Argouarch, G.; Samuel, O.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2891. b) Argouarch, G.; Samuel, O.; Riant, O.; Daran, J.-C.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2893.

15. Marinetti, A.; Labrue, F.; Gene^t, J.-P. *Synlett* **1999**, 1975.

16. Berens, U.; Burk, M. J.; Gerlach, A.; Hems, W. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1981.

17. You, J.; Drexler, H.-J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 913.

18. Maienza, F.; Wo¨rle, M.; Steffanut, P.; Mezzetti, A. *Organometallics* **1999**, *18*, 1041.

19. (a) Nettekoven, U.; Widhalm, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1997**, *8*, 3185. (b) Nettekoven, U.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Widhalm, M.; Spek, A. L.; Lutz, M. *J. Org. Chem.* **1999**, *64*, 3996.

20. Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471.

21. Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3425.

22. a) M. T. Reetz, A. Gosberg, R. Goddard, S.-H. Kyung, *Chem. Commun.* **1998**, 2077; b) M. T. Reetz, A. Gosberg, WO 0014096, 1998 (assigned to Studiengesellschaft Kohle MBH);

23. a. Nettekoven, U.; Widhalm, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Mereiter, K.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 2299. b. Nettekoven, U.; Kamer, P. C. J.; Widhalm, M.; van Leeuwen, P. W. N. M. *Organometallics* **2000**, *19*, 4596. c. Nettekoven, U.; Widhalm, M.;

Kalchhauser, H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. *J. Org. Chem.* **2001**, *66*, 759-770.

24. Barbaro, P.; Bianchini, C.; Giambastiani, G.; Togni, A. *Chem. Commun.* **2002**, 2672.

(a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389. (b) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 371. (c) Hayashi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, *15*, 405. (d) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M. M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Chem. Soc. Jpn.* **1980**, 53, 1138

25. Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, 63, 3511.

26. (a) Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, 62, 6733. (b) Riant, O.; Samuel, O.; Kagan,H. B. *J. Am. Chem. Soc.* **1993**, 115, 5835.

27. (a) Richards, J.; Damalidis, T.; Hibbs D. E.; Hursthouse, M. B. *Synlett* **1995**, 74. (b) Sammakai, T.; Latham H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, 60, 10. (c) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79. (d) Sammakai, T.; Latham, H. A. *J. Org. Chem.* **1995**, 60, 6002.

28. Ganter, C.; Wagner, T. *Chem. Ber.* **1995**, 128, 1157.

29. (a) Enders, D.; Peters, R.; Lochtman, R.; Runsink, J. *Synlett* **1997**, 1462.

(b) Enders, D.; Peters, R.; Lochtman, R.; Runsink, J. *Eur. J. Org. Chem.* **2000**, 2839.

30. Lotz, M.; Ireland T.; Tappe, K.; Knochel, P. *Chirality*, **2000**, *12*, 389.

31. Kitzler, R.; Xiao, L.; Weissensteiner, W. *Tetrahedron: Asymmetry* **2000**, *11*, 3459.

32. Widhalm, M.; Mereiter, K.; Bourghida, M. *Tetrahedron: Asymmetry* **1998**, 9, 2983.

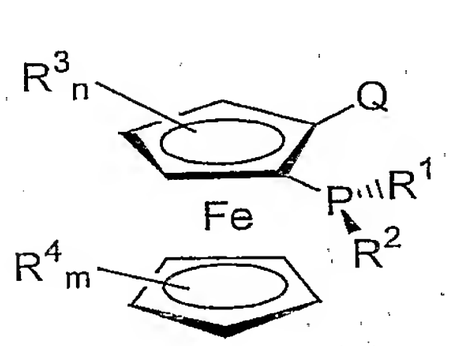
33. Nishibayashi, Y.; Arikawa, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1996**, 61, 1172.

34. (a) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, 118, 685. (b) Jendralla, H.; Paulus, E. *Synlett* **1997**, 471.

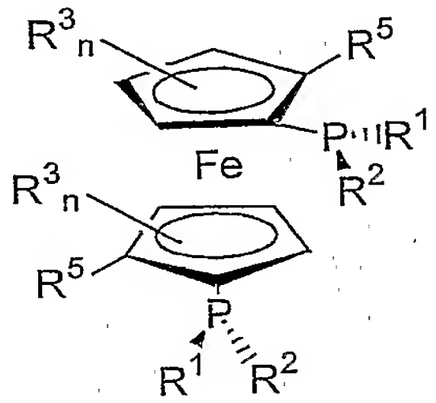
35. Price, D.; Simpkins, N. S. *Tetrahedron Lett.* **1995**, 36, 6135.

CLAIMS

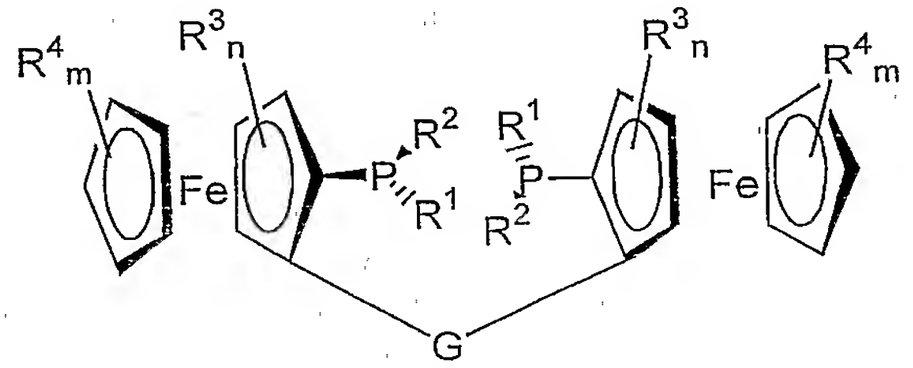
1. A ferrocene-based phosphine ligand chiral at phosphorus having the Formula (I), (II) or (III):



(I)



(II)



(III)

wherein

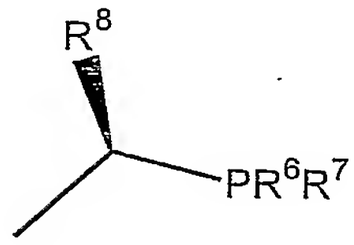
R^1 and R^2 are different from each other, and are independently selected from substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

R^3 and R^4 are the same or different, and are independently selected from substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

n is 0 to 3;

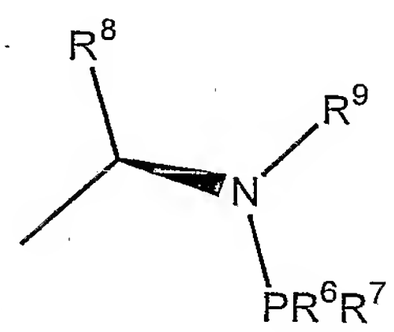
m is 0 to 5;

Q is selected from:



wherein R^6 and R^7 are the same or different, and are independently selected from substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; and R^8 is selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; or

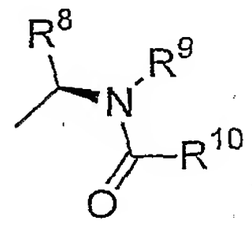
Q is selected from:



wherein R^6, R^7 and R^8 are, independently, as previously defined; and R^9 is selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and

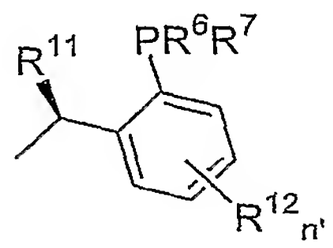
unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; or

Q is selected from:



wherein R^6, R^7, R^8 and R^9 are, independently, as previously defined; and R^{10} is selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; or

Q is selected from:

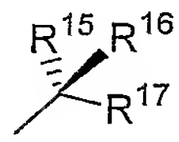


wherein R^6, R^7 are, as previously defined; R^{11} is selected from OR^{13}, SR^{13}, NHR^{13}, $NR^{13}R^{14}$, wherein R^{13} and R^{14} are the same or different and are independently selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and

oxygen; R^{12} is selected from hydrogen, halogen, OR^{13}, SR^{13}, $NR^{13}R^{14}$, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; wherein R^{13}, R^{14} are, as previously defined; and

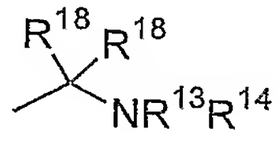
n' is 0 to 4;

R^5 is selected from:



wherein R^{15}, R^{16} and R^{17} are the same or different and are independently selected from hydrogen, OR^{13}, SR^{13}, $NR^{13}R^{14}$, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; wherein R^{13}, R^{14} are, as previously defined; or

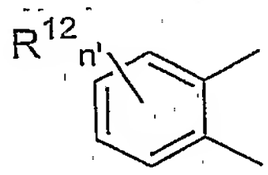
R^5 is selected from:

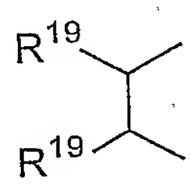


wherein R^{13}, R^{14} are as previously defined; the two geminal substituents R^{18} together are a doubly bonded oxygen atom (i.e. $(R^{18})_2$ is =O), or each substituent R^{18} on its own is hydrogen; and

G is selected from the group consisting of:

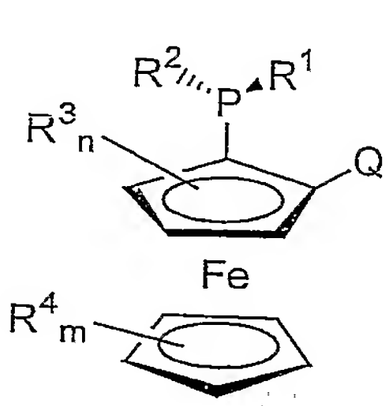
-CONH-R*-NHCO-, -CO-OR*O-CO-, -CO-R*CO-, -CH=N-R*-N=CH-, -CH_2NH-R*-NHCH_2-, -CH_2NHCO-R*-CONHCH_2-, -CH(R^8)NH-R*-NH(CH(R^8)-, -CH(R^8)NHCO-R*-CONHCH(R^8)-, -CONH-R-NHCO-, -CO-ORO-CO-, -CO-RCO-, -CH=N-R-N=CH-, -CH_2NH-R-NHCH_2-, -CH_2NHCO-R-CONHCH_2-, -CH(R^8)NH-R-NH(CH(R^8)-, -CH(R^8)NHCO-R-CONHCH(R^8)-; wherein R^8 is, independently, as previously defined; -R*- and –R- are selected from the group consisting of:



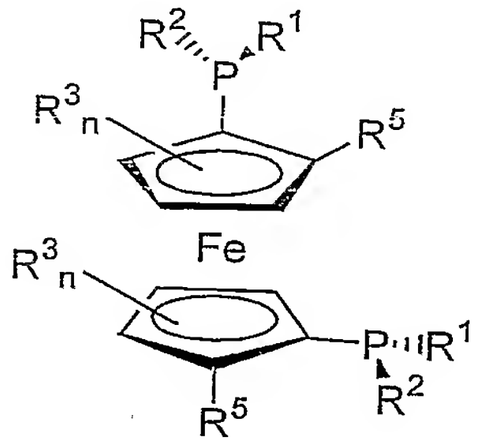


wherein R^{12} is as previously defined; R^{19} is selected from hydrogen, substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen; or $(R^{19})_2$ is -$(CH_2)_{m'}$-, n' is 0 to 4; and m' is 1 to 8;

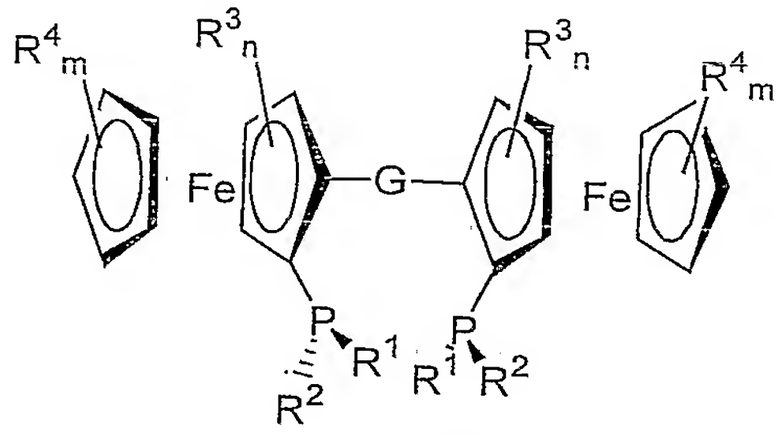
2. Enantiomers of the ligands according to claim 1 having the Formulae (IV), (V) and (VI):



(IV)



(V)



(VI)

wherein each of R^{1-19}, Q, G, n, m, n' and m' have the same meanings as assigned in claim 1, with chirality changes in the substituent groups where required.

3. A ferrocene-based phosphine according to claim 1 or claim 2 having chirality at phosphorus and at least one other element of chirality (planar chirality and/or chirality at carbon).

4. A ferrocene-based diphosphine ligand having three elements of chirality, namely planar chirality, chirality at phosphorus, and chirality at carbon.

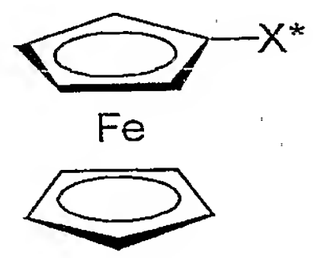
5. Use of the ligand of any one of claims 1 to 4 as a catalyst or catalyst precursor in asymmetric transformation reactions to generate high enantiomeric excesses of formed compounds.

6. A transition metal complex containing a transition metal coordinated to a ligand according to any one of claims 1 to 4.

7. A transition metal catalyst according to claim 6 wherein the transition metal is a Group VIb or a Group VIII metal.

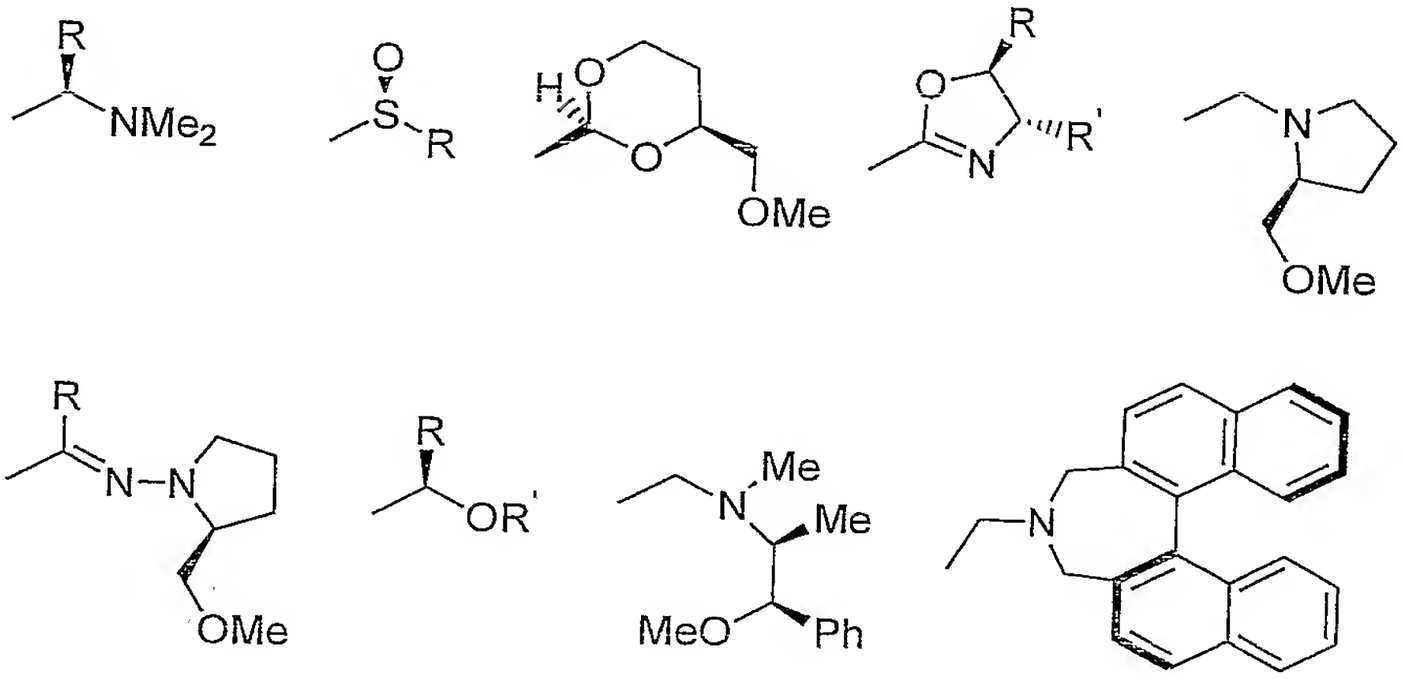
8. A method for preparing a ligand according to any one of claims 1 to 4 comprising providing a ferrocene-based substrate having a chiral directing substituent on one or both rings, and subjecting the substituted ferrocene to an ortho-lithiation followed by converting the ortho-lithiated substituted ferrocene to a phosphine chiral at phosphorus.

9. A method for preparing the ligand of Formula (I) or (III) comprising providing a compound of the formula VII:

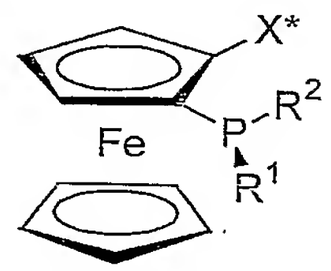


(VII)

wherein X* is chiral directing group, and is selected from the group containing of :



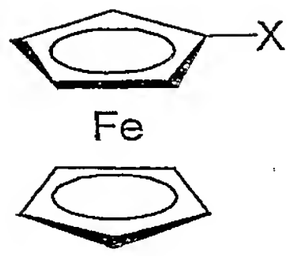
and subjecting the compound to mono-ortho-lithiation using n-butyllithium or sec-butyllithium or tert- butyllithium, and reacting the resulting monolithium compound *in situ* with a dichlorophosphine of the formula R^1PCl_2 followed by reacting with a organometal reagent of the formula R^2M, wherein R^1 and R^2 are as defined in claim 3; M is Li or MgX wherein X is a halide, to obtain phosphorus chiral compound having formula VIII:



(VIII)

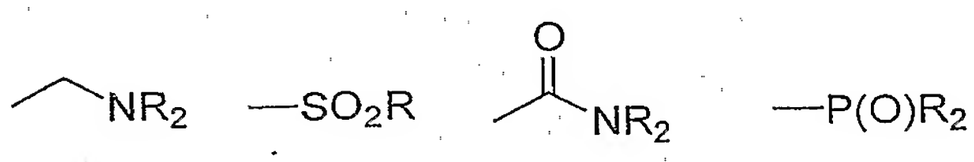
and converting the compound having formula VIII to a compound having Formula (I) or(III).

10. A method for preparing the ligand of Formula (I) or (III) comprising providing a compound of the formula XXXVII:

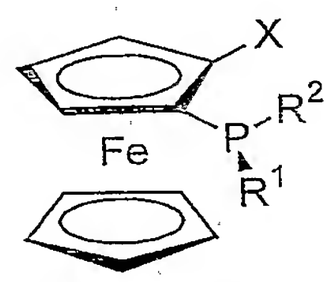


(XXXVII)

wherein X is a chiral directing group, and is selected from:



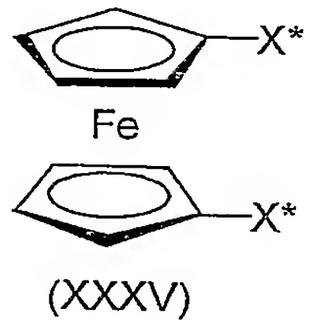
and subjecting the compound to enantioselective mono-ortho-lithiation using n-butyllithium or sec-butyllithium or tert- butyllithium in the presence of a homochiral tertiary amine, and reacting the resulting chiral monolithium compound *in situ* with a dichlorophosphine of the formula R^1PCl_2 followed by reacting with an organometallic reagent of the formula R^2M, wherein R^1 and R^2 are as defined in claim 3; M is Li or MgX wherein X is a halide, to obtain phosphorus chiral compound having formula XXXVIII:



(XXXVIII)

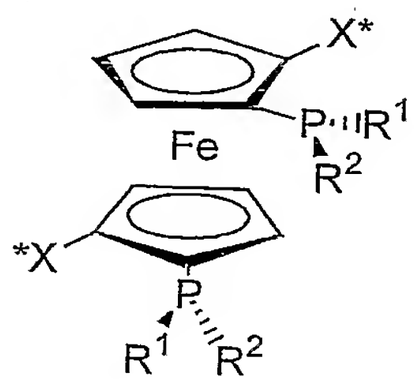
and converting the compound having formula XXXVIII to a compound having Formula (I) or(III).

11. A method for preparing the ligand of Formula (II) comprising providing a compound of the Formula XXXV:



(XXXV)

wherein X* is as previously defined; and subjecting the compound to bis-ortho-lithiation using n-butyllithium, sec-butyllithium or tert-butyllithium, and reacting the resulting bislithium compound *in situ* with a dichlorophosphine of the formula R^1PCl_2 followed by reacting with an organometallic reagent of the formula R^2M, wherein R^1 and R^2 are as defined in claim 3; M is Li or MgX wherein X is a halide, to obtain a phosphorus chiral compound having formula XXXVI:



(XXXVI)

and converting the compound having formula XXXVI to a compound having formula II.

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ABSTRACT

The present invention relates to ferrocene-based phosphine ligands having chirality at phosphorus and at least one other element of chirality (planar chirality and/or chirality at carbon); and to the use of such ligands in asymmetric transformation reactions to generate high enantiomeric excesses of formed compounds. A method for the preparation of ligands according to the invention involving the conversion of the ortho-lithiated substituted ferrocene to a phosphine chiral at phosphorus is also disclosed.